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THE "EOSINOPHILIC GRANULOMAS" OF THE SKIN

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THREE other reports concerning eosinophilic granulomas of the skin appear concurrently with mine in this issue. In them collectively, a full perspective of the world's literature and the history of this disease can be gained, and accordingly these phases of the subject need not be repeated in detail. The same is largely true of the bibliography; the reader is referred to Lever's comprehensive one, which leads into the ten European reports. Incidentally, the reader will be impressed by the abruptness with which the subject has appeared in the American literature and the confusion which exists as to its pathologic significance. Accordingly, this communication can be confined largely to its reports of cases and emphasis on the pathology.

PRIORITY AND NOMENCLATURE

It is important to determine priority because it is necessary in the attempt to establish a definition for eosinophilic granuloma of the skin. According to the laws of priority in general biology, the original employment of a name takes precedence over all other considerations in nomenclature, without exception. On this basis, the so-called original case of Martinotti, published in 1923, does not qualify, because he did not use specifically the term "eosinophilic granuloma of the skin"; Nanta and Gadrat were the first to use the full term, in 1937. For bone, the term "eosinophilic granuloma" was first employed two years later, in 1939, by Finzi. The syphiloid of cats was described as " la syphiloïde du chat (granulome éosinophilique)" by Henry and Bory in 1937. Evidently, then, dermatologists have priority so far as the term "eosinophilic granuloma" is concerned, and the fact that "of the skin" was specified by Nanta and Gadrat in connection with "eosinophilic granuloma" makes it complete. Dermatologists should be careful to use "eosinophilic granuloma of the skin" in full, and surgeons and general pathologists should use "eosinophilic granuloma of bone" in full.

Presidential address delivered at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Hot Springs, Va., June 9, 1946. The paper is modified in view of the fact that other papers on this subject are printed in this issue.

On the basis that Nanta and Gadrat have priority, the characteristics in their case should serve as the type for the disease "eosinophilic granuloma of the skin." Inasmuch as it is a consensus that it is neither an etiologic nor a clinical entity and the histologic features which Nanta and Gadrat postulated are included as type 1 for eosinophilic granuloma of the skin, it remains that the histologic features laid down by Nanta and Gadrat must be accepted as the basis for diagnosis. Inasmuch as monocytes (lymphocytes, plasma cells and histiocytes) are reported in this connection, it would appear that this type of case concerns leukotic disease and belongs in the idiopathic group in the classification which will be indicated later. On this basis, the members of the idiopathic group are the representatives of true eosinophilic granuloma of the skin.

The nomenclature of disease, however, is not so rigid as that in general biology; pathologic processes in tissue are subject to far greater variation "within in the species," as it were, than phases of the structure of plants and animals. It is therefore justifiable to permit a relaxation of the requirements implied by Nanta and Gadrat's original description of the histologic structure and to expand the scope of their findings (and/or modify them) when it appears to be justified. In short, as matters have turned out, these authors inaugurated simply an inquiry into the significance of excessive eosinophilia in cutaneous lesions. The earlier reports of the disease indicate that the authors arrived rather promptly at the conclusion that it was not a clinical or etiologic entity. It revolved in the atmosphere of such diverse leukotic diseases as Hodgkin's disease and mycosis fungoides.

To summarize, dermatology has priority in the use of "eosinophilic granuloma" and Nanta and Gadrat of "eosinophilic granuloma of the skin." The term was used originally by reason of the (eosinophilic) histologic reaction. At present writing, too, it connotes only the processes of eosinophilia. Therefore, the term can be used with the utmost latitude in any dermatosis with great eosinophilia in the tissues. One must not fall into the error that it signifies a specific causation that covers all cases of this pathosis.

As to priority in the literature of this country, credit belongs to Lewis. He was the first to present a case under the particular title of "eosinophilic granuloma"; this was presented at a meeting of the New York Academy of Medicine, Section of Dermatology and Syphilis, on May 3, 1943.[1] My patient was presented on Nov. 17, 1944 before the Philadelphia Dermatological Society.[2]

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1. Lewis, G. M.: A Case for Diagnosis (Eosinophilic Granuloma?), Arch. Dermat. & Syph. **49**:375 (May) 1944.

2. Klauder, J. V., and Weidman, F. D.: A Case for Diagnosis (Eosinophilic Granuloma?), Arch. Dermat. & Syph. **53**:558 (May) 1946.

MATERIALS

Dr. Joseph V. Klauder first stimulated my interest in this subject when he generously placed his patient at my disposal and supplied the clinical photograph and two lots of material from biopsy specimens. This forms the basis of what I shall refer to as "our case." Too, prior to the publication of their papers in this issue, Drs. Lewis and Cormia and also Dr. Lever furnished me with histologic sections and with copies of their manuscripts. Dr. Buley [3] did likewise. The contribution of Dobes and Weidman in this issue speaks for itself. The names of no less than four other physicians will appear later from whom I have received tissues and data which bear on the subject. All these gentlemen have

Fig. 1 (our case).—Lesion of five months' duration (in November 1944, i. e., at the tenth month of the disease).

permitted me to use their materials without reservation and deserve credit as co-authors in this paper; it would be restricted indeed but for their generosity. Altogether, I have been able to study sections from 9 cases.

REPORT OF OUR CASE

The following report extends largely through the first year of the disease. At present it is of two years' duration (as of October 1946), but during the last ten months the patient has passed into other hands.

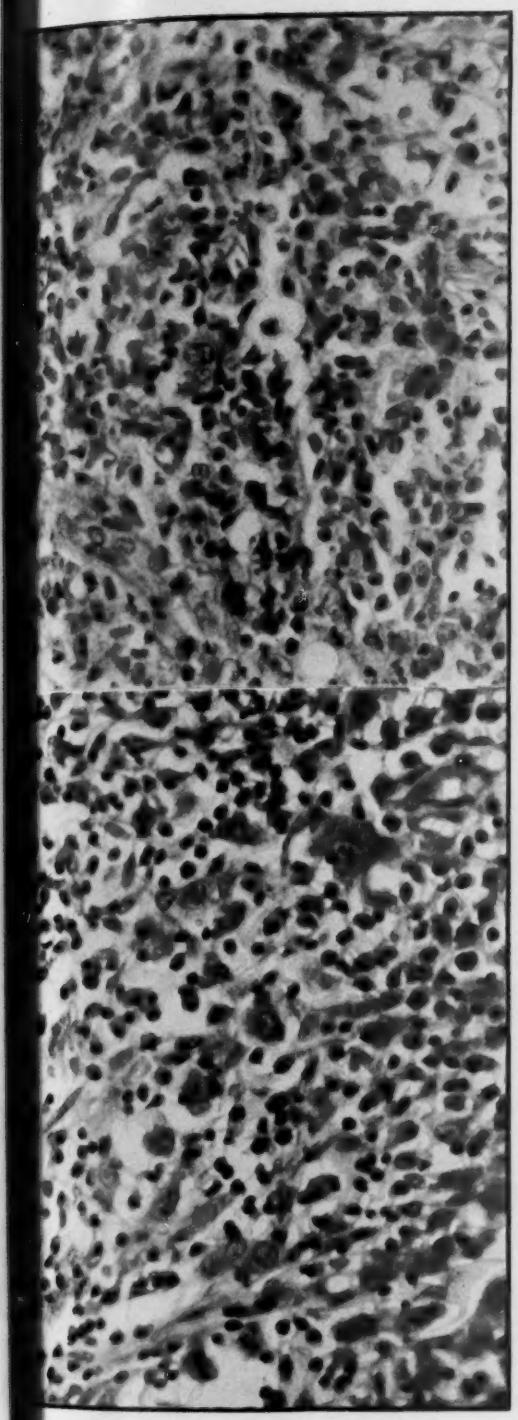
In P. R. H., a white man aged 50 years, there developed a lesion over the right scapula about January 1944. It was treated during March and April

3. Buley, H. M.: Eosinophilic Granuloma of the Skin, J. Invest. Dermat., to be published.

with roentgen rays (1,200 roentgens, divided in six doses, with no filter) by a roentgenologist, and it disappeared. It was reported as being firm, elevated and ovoid, measured 4 by 2 cm. and was centrally ulcerated. Four months later a lesion appeared on the left leg. The roentgenologist administered five doses

Fig. 2 (our case).—The pseudoepitheliomatous hyperplasia. The cellular infiltration was relatively scanty in the upper parts of the skin, as seen here. Deeper, it was densely compacted.

of 1,000 roentgens each, filtered through 0.1 cm. of aluminum. The lesion improved considerably. In June an ulcerated lesion appeared in the left ear. It received 500 roentgens, divided into five doses, unfiltered.



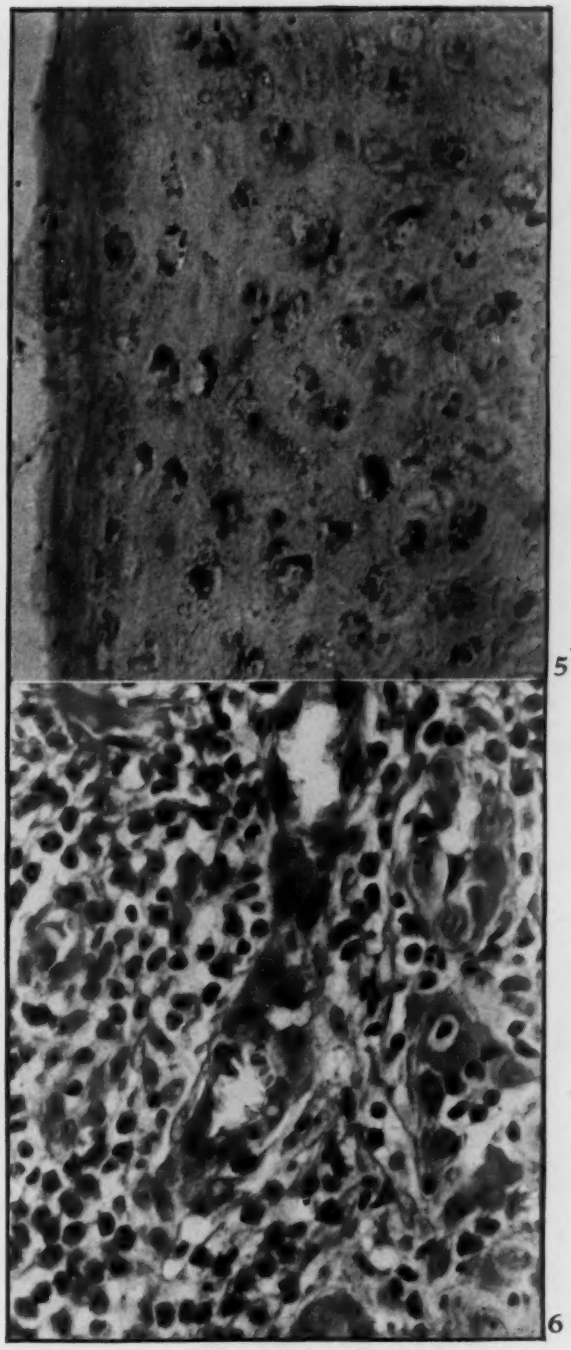


Fig. 3 (our case).—A region of reticuloendotheliosis is exhibited where the monocytes with clear cytoplasms re abundant. Five of them contain mitotic figures.

Fig. 4 (our case).—Another region of reticuloendotheliosis, illustrating the supposedly monocytic cells (reticu- cells?). They fall far short from typical Sternberg-Reed cells.

Fig. 5 (our case).—Sudan III preparation demonstrating fat in the epidermis.

Fig. 6 (Robinson and Ketron's case).—The hyperplastic endothelial cells of the blood vessels are not of the al rounded form that appears in inflammatory reactions.

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I first saw the patient about ten months after the onset of the disease. The concha of the ear was filled by a mass (five months' duration), which concealed the external auditory canal. Its center was ulcerated, bled easily and was covered with a yellowish membrane. Part of the tumor extended onto the anthelix in the form of a plaque with a smooth intact surface, and another portion extended onto the crus helicis. The plaques were firm, elevated up to 2 to 4 cm. above the *niveau* and evidently infiltrated. Under wet antiseptic dressings, the ulcer healed partially and the bleeding became less pronounced. During the subsequent two weeks the mass became larger, and pain developed in the ear, which radiated to the throat and down the neck.

The patient had never traveled beyond the United States; he had not been away from the vicinity of Philadelphia for a number of years. There was no history of syphilis. In November and December, 1,300 roentgens were administered to the ear in twelve doses, and in January 1945 1,000 roentgens was given in ten doses, all of these at 200 kilovolts and with 0.5 mm. copper filtration.

Roentgenograms of the skull demonstrated that the bone underlying the lesion was not involved in the processes, and several roentgenologic examinations of the chest, skull, bones, pelvis, extremities and spine failed to reveal additional lesions. About January 1946, the entire lesion was excised, involving amputation of the ear. Skin grafts did not take. The general physical state of the patient has been steadily downhill since that time, and a fatal termination is expected. A roentgenogram made in April 1946 demonstrated that the lesion had infiltrated into the pterygomaxillary fossa around the roots of the fifth, sixth, seventh, ninth, tenth, eleventh and twelfth cranial nerves. Roentgen treatment (up to 2,700 roentgens) was highly effective at first, but the disease advanced again in August 1946. Up to October 1946, none of the superficial lymph nodes had become enlarged and disease in other parts of the body could not be demonstrated.

The laboratory investigations were not particularly significant. The Wassermann reaction of the blood for syphilis was negative. The red blood cell count was normal, and the hemoglobin content measured 74 per cent. Of the 6,250 leukocytes, only 4 per cent were eosinophils; the other forms were within normal range. The Schilling index showed metamyelocytes 0, stab cells 11 per cent and segmented forms 59 per cent. The multiple index was 3.0, a relatively normal shift. The lesions were not influenced by three intramuscular injections of bismuth subsalicylate and the oral administration of potassium iodide in doses ranging up to 30 grains (2 Gm.) three times daily.

Histologic Examination.—A biopsy specimen was secured on Nov. 10, 1944. The epidermis was ulcerated and acanthotic, highly edematous and sparingly infiltrated with degenerated (apparently neutrophilic) polymorphonuclear leukocytes. The interpapillary pegs were bizarre and extended as long snags to the midcorium. This was an expression of pseudoepitheliomatous hyperplasia, such as occurs frequently in connection with the regeneration of the epidermis in connection with ulceration. The mimicry of cancer was close indeed.

The corium was occupied solidly by inflammatory cellular infiltration, barring an edematous zone which lay immediately below the epidermis. The infiltration was so dense that but little of the normal collagenous tissue could be identified. It was disposed on a reticuloendothelial framework, which was dense in some places but so loose in others as to suggest lattice fibers. Everywhere, blood vessels were extremely numerous, thin walled and sometimes associated with small hemorrhages.

The cells concerned varied from place to place. Lymphocytes and eosinophilic polymorphonuclear leukocytes appeared everywhere, and the latter were so

sharply focalized at some places as to constitute miliary abscesses. An additional type of cell approached the Sternberg-Reed cell closely. It was scatteringly distributed and never in groups. The cytoplasm was rarefied and indeed invisible in some cases. The cell membrane could not be recognized. The nucleus was large and rounded, and a few examples were indented. Many were in mitosis, but, on the whole, they were poor in chromatin. In short, they were probably monocytes which were in a state of hydropic degeneration.

Micro-organisms could not be identified within the abscesses or elsewhere.

A second biopsy was performed on Nov. 15, 1944. Barring certain quantitative differences, the reaction was the same as that in the first biopsy specimen. Thus the degree of eosinophilia was definitely less, although it was still great in one or two localized regions. Mitotic figures were fewer, but the monocytes were much more numerous.

PATIENTS NOT SEEN CLINICALLY BY ME

The patients in the following cases came to my attention as part of the routine histologic work of the laboratory during the two and one-half years which have elapsed since our patient aroused the subject of eosinophilic granuloma of the skin.

CASE 1.—H. J. (a patient of Drs. Harry M. Robinson and Lloyd W. Ketron), a Negro man, was first seen and examined at the University Hospital of the University of Maryland School of Medicine and College of Physicians and Surgeons on July 16, 1945. The duration of his disease was said to have been one month. On the glans penis there were numerous discrete and grouped, round, shiny nodules 2 to 3 mm. in diameter. They were concentrated around the urethral orifice and the corona. A slight, dark red discharge escaped from the urethra. The cystoscope passed easily; the prostatic urethra was found to be congested and the verumontanum engorged and bleeding. It was the urologist's impression that verumontanitis was present. The serologic test of the blood for syphilis elicited a negative reaction. Both the Frei and the Ito-Reenstierna test gave positive reactions. The white blood cells numbered 10,150 and the red blood cells 4,970,000. The polymorphonuclear neutrophils constituted 27 per cent, the lymphocytes 55 per cent and the eosinophils 18 per cent. The hemoglobin content measured 16.1 Gm. The sedimentation rate was 40 mm. corrected to 34. The hematocrit reading was 46 per cent.

Microscopic Examination.—A biopsy was performed on Nov. 19, 1945. Two types of pathologic change were represented in the tiny nodule. The first process was an extensive hyperplasia of highly dilated capillaries, which was so extreme as to suggest endothelioma. However, the blood vessels were distributed regularly and uniformly throughout the lesion and were uniformly spaced and normally formed. Moreover, the lining endothelial cells, although hugely enlarged, were disposed at regular intervals in a single layer over the linings of the capillaries. They were striking by reason of their huge size, broad cytoplasms and polygonal outlines. They were not crowded or at all anaplastic, such as should be the case for endothelioma. In short, the huge enlargement of the individual cells was accompanied with comparatively little numerical increase.

The second process consisted in an extreme, diffuse infiltration of eosinophilic polymorphonuclear neutrophils. There was not any noteworthy connective tissue or other kind of stroma.

Summary and Interpretation.—A localized nodular eruption on the glans penis of one month's duration, which may or may not have had a relationship to associated disease of the prostatic region, had a certain resemblance clinically to molluscum contagiosum. The reactions of the tissue were most puzzling, but hemangioendothelioma appears to be excluded. The uniformity and individuality with which the endothelial cells are reacting appears to exclude an inflammatory causation for the hyperplasia and points more reasonably toward some leukotic factor. The extreme eosinophilia is the only feature which suggests any relationship to eosinophilic granuloma of the skin.

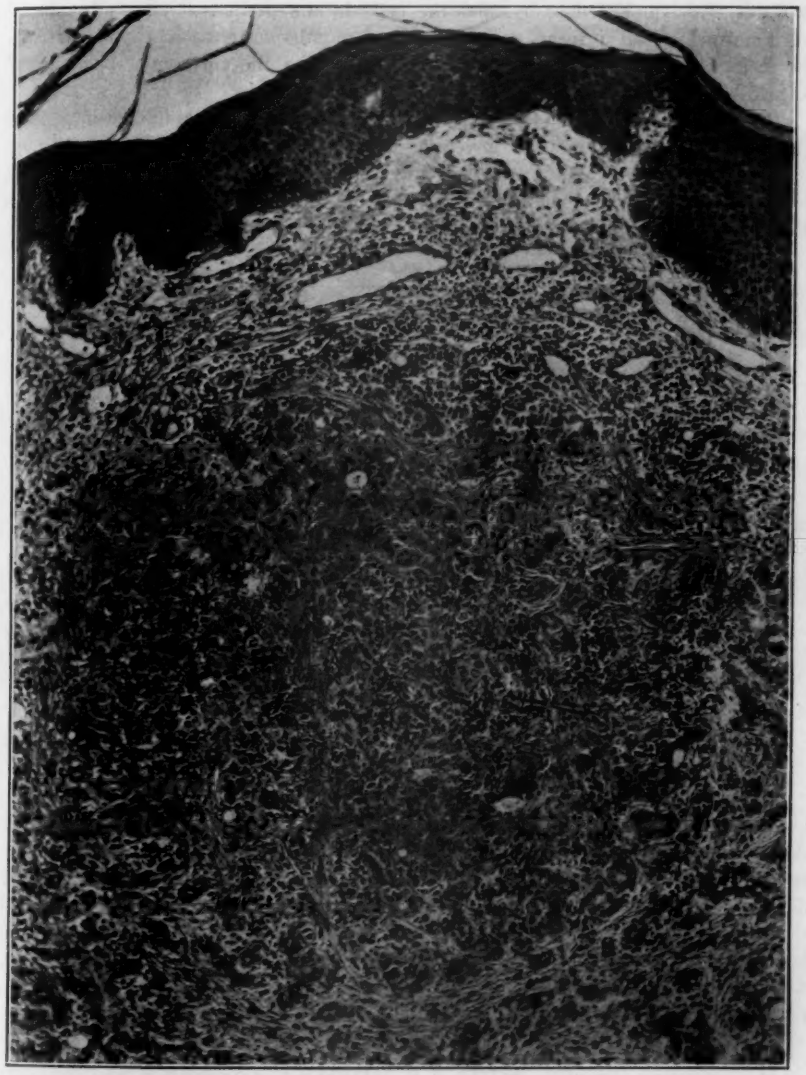

Fig. 7 (Robinson and Ketron's case).—The angiomatoid patterning.

Case 2.—A white woman (a patient of Drs. Earl Runyon Tyler and John D. Miale), aged 26 and in excellent health, observed first a nodule over the left eyebrow in August 1945. It enlarged slowly, became purplish red and was slightly itchy. Subsequently, lesions appeared scatteringly over the body but with a predilection for the arms and face. They were still slightly itchy, attained a diameter of about 2 cm. and eventually disappeared, leaving only a slight induration. There was not any lymphadenopathy, and the cells in the peripheral circulating blood were normal in all respects. During three months of treatment with arsenic, the lesions disappeared, leaving a solitary lesion on the forearm. The clinical features were only suggestive of mycosis fungoides.

Microscopically, the epidermis was decidedly acanthotic and exhibited in general the (edematous) features of mycosis fungoides but without any Pautrier's abscesses. The processes in the corium were not those of mycosis fungoides. There was not any reticuloendothelial network, and the infiltrating cells were not disposed in the widespread way that is usually the case for mycosis fungoides

Fig. 8 (Robinson and Ketron's case).—Lesions on glans penis.

but were confined within mantles around the blood vessels and appendages. At two places, though, they infiltrated the subcutaneous fat. Although lymphocytes appeared in a few localized regions, eosinophilic polymorphonuclear neutrophils dominated the scene; they were massed in the places where the infiltration was the more extensive, particularly toward the subcutaneous fat. A few hyperplastic endothelial cells and certain other large cells, which were presumably monocytes, were intermingled. It was not possible to identify any indented or reniform nuclei such as would prove the presence of monocytes.

Summary and Interpretation.—In the absence of generalized lymphadenopathy or of an adequate histologic picture, it is hazardous to pronounce a final diagnosis of mycosis fungoides to say the least, and the absence of severe itching adds to the uncertainty. The disease was probably of the order of a low grade cellulitis. This case is included in my series as a matter of record in connection with eosinophilic granuloma of the skin and because mycosis fungoides was seriously considered by Lapiere in his case. In any event, the eosinophilia was impressive to say the least.

CASE 3.—C. C. (a patient of Dr. Louis Goldstein), a white woman aged 38 and single, had suffered from deep-seated papules on the upper and lower extremities for seven years. They underwent superficial ulceration and disappeared, leaving pigmented macules.

A biopsy was performed on April 21, 1945. Microscopically, a localized area of reticulosis was observed in relation to a hair follicle. Young blood vessels ramified richly through it. Most of the cells in the case were lymphocytes, but polymorphonuclear eosinophils predominated in certain regions. Typical Sternberg-Reed cells were sparingly intermixed. The eosinophils did not appear in the tissue surrounding the granuloma; here only a heavy mantle of lymphocytes appeared around the blood vessels.

A second biopsy was performed May 26, 1945 on the back of the right leg. By this time a solitary lymph node in the axilla had become enlarged, and up to October 1946 it remains the only one. The reaction differed from that in the first biopsy specimen in that the regions of polymorphonuclear infiltration were more numerous and that the histiocytes were seldom of the typical Sternberg-Reed type. The appearances were not nearly so convincing for Hodgkin's disease as those in the first specimen. Indeed, considered purely from the histologic viewpoint, they were not even suggestive.

Further biopsies were performed on May 4, 1946 on material from lesions on the inside of the right thigh and the front of the left forearm. At this time the lesions were prurigo-like. Singularly, in neither of the lesions was there enough eosinophilia to attract attention. A remarkably heavy mantle of reticulo-endothelial tissue comprised broad tracts around certain blood vessels in the midcorium. The cells were largely lymphocytes, but reticulum cells were also abundant. Monocytes could not be identified. Only a few small clusters of polymorphonuclear neutrophils were widely scattered here and there. In sections stained by Giemsa's method, a few mast cells were brought to light but gave no additional information. Neither in the lesion from the forearm nor in the lesion from the leg were there any of the features of Hodgkin's disease or eosinophilic granuloma. In short, at this stage of the disease the leukotic processes of Hodgkin's disease appeared to be quiescent, at least in the skin. Apparently such processes occur in waves, and accordingly the histologic picture varies from time to time.

Summary and Interpretation.—This case should be regarded as one of Hodgkin's disease in which the cutaneous lesions clinically were of the non-specific type, i. e., prurigo-like. The histologic picture of Hodgkin's disease was exhibited satisfactorily only in the first biopsy specimen; the development of lymphadenopathy was necessary to establish the diagnosis.

CASE 4.—Mrs. von T. (a patient of Dr. Carroll S. Wright) presented an ulcerated lesion on the vulva, which had been present for one year. It had a slightly elevated border. The Wassermann reaction of the blood was negative on several occasions, and cultures had been made which were without significance. Examinations of the peripheral circulating blood resulted in normal findings. Dr. Wright removed the lesion by cauterization on March 28, 1945; this was followed by healing. Two lesions developed subsequently which were also cured by cauterization.

Microscopically, a quasituberculoid reaction was observed in the base of the ulcer. It constituted a superficial zone, underlaid by a remarkable infiltration by eosinophilic polymorphonuclear leukocytes (no eosinophilic myelocytes). Scarcely a neutrophilic leukocyte could be discovered anywhere in the section.

The tuberculoid tissue consisted of solidly packed "epithelioid cells," but in no case were they localized into miliary granulomas and there were not any giant cells. Some of the epithelioid cells were indented or reniform, and a few were in mitosis. The endothelia of the blood vessels were swollen, but, in spite of the fact that a few mitoses were occurring in them, they were not notably hyperplastic. A few foci of necrosis were not surrounded by the special zones of cells, such as is characteristic for tuberculosis.

A third lesion was excised on Sept. 15, 1946. Fixed in solution of formaldehyde it was definitely yellow, but it was not adequate for frozen sections and staining for lipids. The order of reaction was that of the first lesion, with certain quantitative differences. Lymphocytes were confined to positions adjacent to blood vessels. Now the monocytes were so closely packed that a reticuloendothelial framework could scarcely be recognized. The nuclei of some were huge, others were indented or reniform and some were in mitosis. Contrary to the first lesion, neutrophilic leukocytes were in a large majority. Eosinophils, some of which were mononuclear and others polymorphonuclear, occurred only in nests here and there throughout the lesion, i. e., they were not nearly so numerous as in the first biopsy specimen. The lumens of blood vessels, although crowded with eosinophils, did not contain any monocytes. The reaction was not at all tuberculous; it stimulated aleukemic reticulosis, but with eosinophils. This was evidently an older lesion, because the infiltration extended much more deeply and the polymorphonuclear cells were far fewer.

Summary and Interpretation.—A histologically tuberculoid lesion of the vulva, accompanied with extreme eosinophilia of the tissues, may or may not have been the expression of most atypical, diffuse tuberculosis in which the monocytes assumed a form other than that of the typical epithelioid cell. However, the indented and reniform nuclei are foreign to tuberculosis as it is conventionally conceived. This case is included in my series largely because the monocytes in the case took a quasiepithelioid form similar to the ones which have been described by Dobes and Weidman in this issue in one of the lesions of their patient with Hodgkin's disease. In eosinophilic granuloma of bone, too, the monocytes can assume this form.

ANALYSIS AND CLASSIFICATION

The cases which have been published in the literature have already been abstracted and discussed in the papers by Lever and by Lewis and Cormia in this issue. There is general agreement that the clinical picture is so variable that it cannot serve of itself either as a basis for diagnosis or as the establishment of an entity. In every case, it was the eosinophilia which originated the diagnosis. The same must be said of the 5 patients whose case histories are recorded herein.

The details of the histologic features, too, have been sufficiently covered by Lever and by Lewis and Cormia. The histology is far more constructive toward the establishment of an entity than through clinical channels. It will be noted that there are but two features common to all the cases, namely the deep location of the lesions and the eosinophilia. Thereafter, histiocytes received mention frequently; incidentally, it is probable that some of them were numbered among the "eosinophils" simply by reason of the eosinophilic granules that they phagocytosed

after such granules had escaped from other kinds of cells. Polymorphonuclear neutrophils were described less frequently (Dobes and Weidman and Martinotti's third case). Monocytes received frequent mention, but, inasmuch as this type of cell can be interpreted on such a variable basis at the hands of different authors, the significance of all the monocytes cited is indefinite indeed. Still, there can be no question that they were frequently concerned. Eosinophilic myelocytes were included by Pasini and plasma cells by Freund. The "monstrous cells" described by Lapiere could have been of the same order (monocytes) as those described by Dobes and Weidman, and, inasmuch as Lapiere found a picture in the lymph node which resembled that in Hodgkin's disease, it is possible that both of the cases were in fact ones of Hodgkin's disease. I found epithelioid cells in Wright's patient and in one of the lesions in the case of Dobes and Weidman.

In short, the types of cells are indeed diversified, but the pleomorphism is of a different order from that of mycosis fungoides. This is not surprising in cases in which cells of the reticuloendothelial system are concerned; there are similar variations within one and the same entity, such as illustrated by Hodgkin's disease. Accordingly, a definite formula for cells must not be insisted on for the diagnosis of eosinophilic granuloma of the skin.

Suppuration.—Suppuration was conspicuous by its absence in both the clinical reports and the histologic sections. It is not surprising when one considers the small numbers of neutrophilic polymorphonuclear cells that appear in the sections, although the eosinophilic ones can occur in such large and solid masses that they qualify as eosinophilic abscesses. The latter term must be modified at once though, because liquefaction is not in evidence; they would have to be "dry abscesses."

An explanation of such dryness is at hand because eosinophilic polymorphonuclear cells do not produce the proteolytic (liquefactive) enzymes in human beings in the way that the neutrophil ones do. It is worth while to compare this situation with that in birds. In these, clinical suppuration is practically unknown, even in diseases that are known to be of the most acute infectious nature and in which suppuration would be expected if it were mammals that were affected. Suppuration is replaced by caseous material. Veterinarians advance the similar explanation for this dryness, namely, an absence of proteolytic enzymes in the eosinophilic leukocytes which dominate the picture, but they extend the idea to include the neutrophilic ones.

Thereafter, features other than the cytologic are available and must be drawn on for purposes of evaluation of the processes, such as the patterning of the pathologic tissues, vascular relationships and reticuloendotheliosis; these, especially the latter, are of surpassing value. With their help, I have ventured to arrange a histologic classification such as

is indicated in the table. The classification is based on the fact that some of the conditions, at least, exhibit reticuloendotheliosis and might be leukotic in nature, in the sense of Hodgkin's disease. In a second category, certain cases are included in which there is not any reticuloendotheliosis; the eosinophilic leukocytes are simply exudative (or histiogenetic?) and not associated with monocytes or other cells which might signify a leukotic factor in the case. In some of the cases, the evidence is clearcut; for example, unequivocally reticuloendothelial conditions are illustrated in those of Pautrier and of Dobes and Weidman and the "symptomatic" ones in the case of Lewis and Cormia. They

Classification of Eosinophilic Granulomas of the Skin

A. Idiopathic (leukotic)	
1. Eosinophilic myelopoiesis only; theoretic, and cases may never be established; an aleukemic myelogenous leukemia that is dominantly eosinophilic	
2. Endotheliosis with eosinophilia	(Robinson and Ketron's case)
3. Reticuloendotheliosis with eosinophilia Hodgkin's disease (with lipoidosis)	(Dobes and Weidman's case) (Goldstein's case)
Mycosis fungoides or Hodgkin's disease	(Lapiere's case)
Mycosis fungoides (atypical)	(Freund's case)
Lymphosarcoma	(Cerruti's case)
Aleukemic reticuloendotheliosis	(Pasini's case)
Aleukemic reticuloendotheliosis with lipoidosis	(Our case)
B. Symptomatic (inflammatory, including specific granulomatous infections)	
1. Erythema multiforme perstans (Loeffler's syndrome)	(Lyon and Kleinhaus)*
2. Ids, with eosinophilic periarteritis	(Lewis and Cormia's case)
3. Erythema elevatum diutinum	(Lever's case) (Buley's case) (Wigley's case)
4. Orificial tuberculosis	(Wright's case) (Nanta and Gadrat's case)
5. Specific infections (syphiloid of cats)	(Bory)
6. Nonspecific ulcer of the leg	(Martinotti's case 1)
7. Yeast infection	(Martinotti's case 2)
8. Bullous erythema multiforme ?	(Martinotti's case 3)
9. Cellulitis ?	(Tyler and Miale's case)
10. Not diagnosable	(Pautrier's case)

* Not known that the cutaneous lesions were eosinophilic. This remains to be shown.

may serve as type cases. Inadequacy of histologic descriptions prevents a satisfactory, clearcut assignment of some of the cases reported.

I am encouraged to employ this basis for classification because two of the so-called lymphoblastomas, namely, mycosis fungoides and Hodgkin's disease, have been implicated already by Pautrier and by Lapiere. Moreover, Lewis and Cormia have taken a forward step by segregating their case as one of eosinophilic periarteritis; it would fall into my "symptomatic" group. In any event, my classification may serve as a point of departure for the further appraisal of eosinophilic granuloma of the skin. The limitations imposed by the difficulty of histologic interpretation within the field of the leukoses speak for an uncertain basis for appraisals in any circumstances, and accordingly the

classification submitted cannot be perfect in expressing a true biologic situation. It is to be emphasized that the classification is only a working plan.

After having postulated the idiopathic and the symptomatic groups of cases, I have taken a step farther. Thus, by combining the clinical and the histologic features, I have attempted to identify some already established dermatologic entity in the case but to which eosinophilic features have been added. In the idiopathic group the case of Dobes and Weidman serves as an example in which it was Hodgkin's disease to which the eosinophilia was added, and for the symptomatic group Lever's case of erythema elevatum diutinum may be taken as the type. The line of reasoning would parallel here the one which I have followed in studies of xanthoma. To cite but one example, it is thoroughly established that the histologic picture of xanthoma may devlop within scar tissues [4] to the extent, indeed, that the original scar tissue in the sections is not recognizable. That is, only the clinical history of a preexisting scar established the case. In other words, it is conceivable that in eosinophilic granuloma of the skin, too, an intercurrent eosinophilous disease or at least pathologic substrate can modify or obscure an otherwise readily diagnosable entity.

The message to be derived from this theory is that in future studies of eosinophilic granuloma of the skin this possibility should be reckoned with. I do this in spite of Buley's opinion that it would add confusion. I would submit that, as I have plotted out the 19 cases in my classification, an illustration is supplied as to the diversity, at least, of conceivable dermatologic pathoses within which the syndrome of eosinophilic granuloma might occur; in this light, the dermatologist should not be hesitant in maintaining his clinical diagnosis of some well known entity simply because the eosinophilic syndrome appears in the sections. Indeed, it is predictable that additional dermatoses will be placed on the list. Moreover, it was in this light that an over-all view of the cases permitted the two major subdivisions in the classification, and, after the two different pathologic bases which are concerned (leukotic and inflammatory) are revealed, it becomes obvious that the prognosis is radically different in the two.

Buley's discussion of Sulzberger concerning histamine is welcome here in helping to explain some of the discrepancies that arise in eosinophilic granuloma of the skin, "such substances capable of producing a dense eosinophilic infiltrate as those described might well alter the clinical manifestations of a well known entity to such a far reaching

4. Weidman, F. D., and Boston, L. N.: Generalized Xanthoma Tuberosum with Xanthomatous Changes in Fresh Scars of an Intercurrent Zoster, Arch. Int. Med. **59**:793 (May) 1937.

extent that the typical character of a certain disease would be partly or entirely lost." The point is that in the presence of such disturbing factors well known entities would become more readily admissible as such (in spite of their diagnostic shortcomings) when complicated by the eosinophilic syndrome.

The application of the foregoing facts in the diagnosis from histologic sections is clear. Thus, when the eosinophilia is so great as to arouse thoughts of eosinophilic granuloma of the skin, the attempt should be made to determine whether the associated reaction is the reticuloendothelial one or the perivascular one. The former will at once connote the considerations recorded for the idiopathic group and the perivascular ones those of the symptomatic. In the case of reticuloendothelial reactions, the attempt should be made to determine whether it is inflammatory or leukotic; this is usually a difficult task, and there should not be any hesitation in consulting the expert hematologist.

SIGNIFICANCE AND ROLE OF THE EOSINOPHILIA

For the purposes of this communication the contributions of Lever and especially of Lewis and Cormia in this issue supply adequate outlines of the circumstances in which eosinophilia in general may occur. The literature is gigantic, but a perspective of the whole situation has been supplied by Ringoen.[5] It is clear that an eosinophilia of the blood can arise in many different ways, but unfortunately the literature is not nearly so satisfactory in respect to eosinophilia in the fixed tissues. However, it has long been an accepted fact that eosinophilia both of the blood and of the fixed tissues has been conspicuous where cutaneous disease was concerned. The significance of this is not known, but the importance of the skin in allergic processes and the eosinophilia which is so conspicuous in allergy must have a bearing in the situation. In any event, there are agencies extant for inducing eosinophilia in both the idiopathic (reticuloendothelial) and the symptomatic (inflammatory) groups indicated in my classification. It is not necessary to elaborate in the case of the former group because it already implies a lesion of hemopoietic tissue where myelopoiesis (including eosinophilia) can be taken for granted.

In the case of the symptomatic group though, it is recommended that in the future the studies of Buley be followed as a pattern in an attempt to discover an underlying cause for the eosinophilia. Too, in view of the frequency with which authors have quoted both mononuclear and polymorphonuclear eosinophils in the skin, the attempt should be made to establish the identity of the ones which were designated as

5. Ringoen, A. R.: Eosinophile Leucocytes and Eosinophilia, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 1, p. 181.

"mononuclear." Are they monocytes or what? Inasmuch as the details of these cells are inadequate in histologic sections, it is recommended that impression preparations of tissues be made, such as have been urged by Winer [6] in the study of Hodgkin's disease. This is highly important to dermatologists; by such a procedure much might be learned in respect

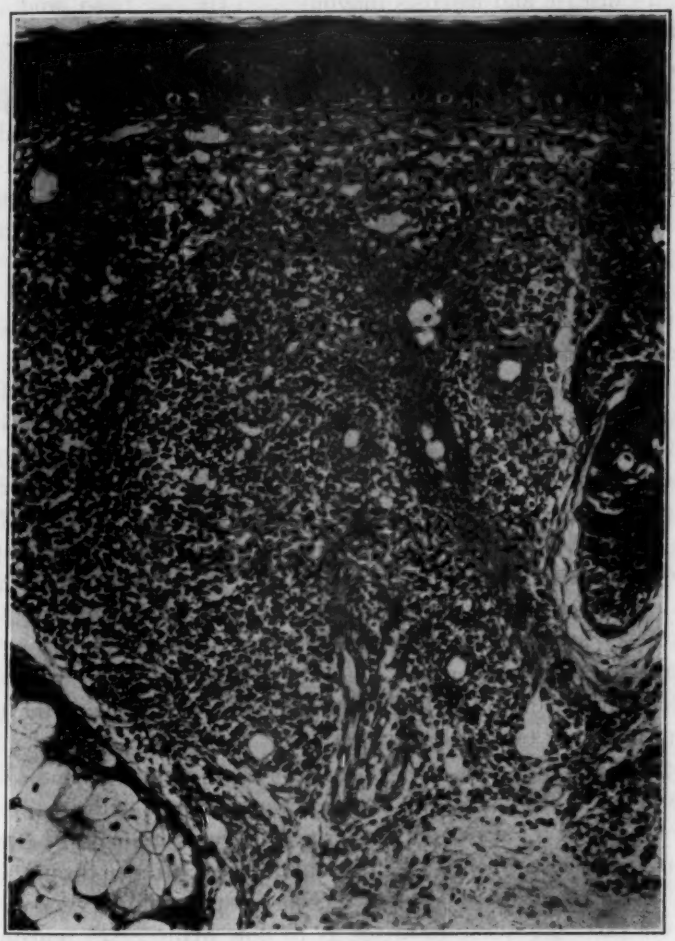

Fig. 9 (Buley's case).—The type of reaction in the symptomatic group, i. e., no reticuloendotheliosis but a vasculitis and perivasculitis.

to an unsuspected leukotic role. The studies should be conducted along the same lines that a hematologist follows for essential disease of hemopoietic tissue.

6. Sweitzer, S. E., and Winer, L. H.: Ulcerative Hodgkin's Disease and Lymph Node Imprints, Arch. Dermat. & Syph. **51**:229 (April) 1945.

In consideration of eosinophilic granuloma of the skin in all its aspects, although it is neither an etiologic nor a clinical entity, it is proper to set it up as a histologic entity or syndrome in the setting of eosinophilia. Thus, it satisfies the definition of an entity because the eosinophilia is so extreme and because even at this early date in its history it has been found to revolve around leukotic conditions like Hodgkin's disease and mycosis fungoides, on the one hand, and around arteritis (Lever, and Lewis and Cormia), on the other. In all probability, other categories of dermatologic disease will be added. It is an entity within the histologic field in the same sense that erythema nodosum and erythema multiforme are entities within the clinical field. For example, in erythema multiforme the etiologic factor is not a single one; there is much variation in the distribution of lesions in the case and even in the appearance of the lesion, and yet the ensemble contains sufficient characteristics to identify it as an entity.

In short, the concept of eosinophilic granuloma of the skin as an entity is a useful one if nothing else. Its occurrence points along certain definite avenues which should be followed toward the discovery of an etiologic factor. On the other hand, its limitations must be definitely understood. It is only a tissue eosinophilia, but it still has disease associates that are significant. It is not etiologically diagnostic. It does not connote any special order of tissue process that is peculiar to any clinical entity of the skin, such as is the case for eosinophilic granuloma of bone, unless investigations of the future prove otherwise. I have employed "eosinophilic granulomas of the skin" (i. e., in the plural) in the title of this paper because most physicians will desire a term that will cover the pathosis in all its aspects: etiologic, clinical and histologic; this communication is an example of a situation in which "granulomas" is indicated. When discussing an individual case, it is "one of the eosinophilic granulomas of the skin."

Both in the literature and in some of my personally studied cases, the eosinophilia has not been constant, either in blood or in tissue. This appears to speak for waves of the eosinophilogenic influences. Naturally this introduces its problems; a biopsy performed at the appropriate stage would reveal no eosinophilia, and the diagnosis would be missed. Such being the case, the question arises as to how many cases remain undiagnosed or are regarded as Spiegler-Fendt sarcoid and other such vague expressions of leukotic disease. It is not clear whether the waves of eosinophilia coincide consistently with the regression of the lesions.

It is curious that the subject of eosinophilic granuloma of the skin should have been so suddenly introduced into dermatology in the United States. Probably the recent publicity for eosinophilic granuloma of bone is mostly responsible, but it still remains that the eosinophilia is so striking that it ought to have aroused comment years ago. The familiar

question in medicine at large now arises: "Is this in fact a new disease, or has it simply been overlooked?" Only a laborious study of dermatologic histologic files can supply the answer. In any event, attention should be focused on newer factors in the life of the population which might be bearing an influence on its tissues, especially the hemopoietic ones. The sulfonamide drugs, barbiturates, aminopyrin and ethyl lead are in point. These are worth while covering when the clinical history is being elicited.

RELATIONSHIP TO EOSINOPHILIC GRANULOMA OF BONE, LOEFFLER'S SYNDROME AND THE SYPHILOID OF CATS

Eosinophilic Granuloma of Bone.—Lesions of the bone and skin in the same patient have been reported but once. Gross and Jacox [7] simply stated that their 4 year old patient with eosinophilic granuloma of bone had two small intracutaneous plaques in the left eyelid, but a cutaneous lesion apparently was not examined histologically and it is not known whether it was eosinophilic. It may have been a xanthoma. I agree with Lever and with Lewis and Cormia that there is not any proof at present that eosinophilic granuloma of bone is related to that of the skin. If there is any connection, it could be established only in a most roundabout way, i. e., through transitional forms of Letterer-Siwe and Hodgkin's diseases, such as was indicated by Dobes and Weidman. If this mechanism should obtain, it would occur within the idiopathic group of the cutaneous eosinophilic granulomas (containing Hodgkin's disease and other reticuloendothelioses).

Loeffler's Syndrome.—In Loeffler's syndrome, though, there are real possibilities of a relationship with eosinophilic granulomas of the skin. In connection with pulmonary symptoms which sometimes suggest tuberculosis, the roentgenologist has discovered transitory banal infiltrations in the lungs, and necropsy has demonstrated that they contain great number of eosinophils (von Meyerburg). Sometimes they affect an entire lobe. They are fleeting indeed, lasting but three to eight days. The eosinophilia of the blood ranges from 8 to 66 per cent. The journals of tropical medicine are outstanding in their reports of this disease because animal parasites (ranging from Ascaris to Amoeba) are the occasion for the eosinophilia; Hodes and Wood [8] called it "tropical eosinophilia." Indeed, the injection of extracts of Ascaris has proved the eosinophilogenous role of these parasites through the mechanism of allergy. The interstitial tissue (not the bronchi) is the shock

7. Gross, P., and Jacox, H. W.: Eosinophilic Granuloma and Certain Other Reticulo-Endothelial Hyperplasias of Bone, Am. J. M. Sc. **203**:673 (May) 1942.

8. Hodes, P. J., and Wood, F. C.: Eosinophilic Lung (Tropical Eosinophilia) Am. J. M. Sc. **210**:288-295 (Sept.) 1945.

organ.[9] However, animal parasites are not always demonstrable, notably in the cases in Palestine and those in which cutaneous manifestations were associated.

Cutaneous involvement has been established by Lyon and Kleinhaus.[10] They reported 20 cases in Jerusalem in six months, although several patients did not exhibit pulmonary lesions. They cited other authors, who spoke of "eosinophilic erythroedema" and "eosinophilic disease with cutaneous manifestations" and of eosinophilia in the sternal bone marrow in addition to the other lesions. Substantially, the dermatosis qualifies as a diffuse erythema multiforme perstans in large patches, affecting both the skin and the oral mucosa and often migrating. It does not have any significant distribution. The onset can be as sudden as in angioneurotic edema. It is regrettable, to say the least, that a biopsy was not performed on a specimen of the skin, because it would serve as a base line for evaluation of the other eosinophilic granulomas of the skin. Inasmuch as their publication may not be readily accessible, the following excerpt is supplied from their communication:

> Swelling of the skin develops somewhere partly heralded by prodromi, such as general malaise, desire for sleep, pain in the chest, abdomen or back, partly out of perfect health, usually without or only with insignificant elevation of temperature. The skin over these areas may be oedematous but may also be red, hot, resembling urticaria or erysipelas, lymphangitis, or it may also appear in the shape of a boil. The swollen areas may show great variation in size, distribution and localization. Occasionally the same region is several times attacked. The swelling may be diffuse, spreading over an entire arm but may also be small and irregular in shape. There are itching, tension and pain of a varying degree. A sensation of heaviness of the feet may render walking difficult, or may, if it appears in the arms, hinder the patient in his work. A characteristic feature is the migratory character of the swellings which may persist from 2-8 days, or even longer. In one case swelling of the arm continued to be present for almost seven weeks. Only in one case was a subcutaneous nodule discovered in the skin of the shoulder. Two cases presented swelling of the cervical lymph nodes, two swelling of the mucous membrane of the mouth persisting for a few days, and in one case there was oedema of the eyelid. Part of the patients feel quite comfortable, others experience a certain discomfort and are unable to work.
>
> With only one exception, the blood contained an increased amount of eosinophils (7-50 per cent), there is further leucocytosis (8,000-15,000). The blood sedimentation is normal or slightly accelerated. The red cell count is normal. In our cases the migratory and recurrent swellings of the skin, accompanied by eosinophilia of the blood, persisted for several weeks, occasionally 2-3 months. The affections is not dangerous but troublesome.

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9. Transitory Pulmonary Infiltrations Associated with Eosinophila (Loeffler's Syndrome), editorial, J. A. M. A. **126**:837 (Nov. 25) 1944.

10. Lyon, E., and Kleinhaus, E. M.: An Eosinophilic Disease with Cutaneous Manifestations Associated with Transitory Pulmonary Infiltration (Loeffler's Syndrome), Acta med. orient. **4**:144-149 (May) 1945.

This syndrome may be highly significant for the mechanism in the symptomatic group of eosinophilic granulomas of the skin such as I have outlined in previous pages. There is here a clearcut illustration of a proved specific agent (the animal parasite in some cases) which induces interstitial eosinophilic masses. Whether it occurs in a focus of preexistent congestion or bronchopneumonia remains to be demonstrated, but if such were the case (and it is possible) it would indicate by analogy that the eosinophilic infiltrations in the skin could develop through a similar pathologic mechanism. It would be illuminating indeed to study histologic sections of some of our typical dermatoses such as erythema nodosum and even tuberculosis and learn whether they too were unduly eosinophilic as they occurred in the tropics and in the presence of animal parasitic disease. Or would the experimental induction of eosinophilia in human beings or animals result in a histologic modification of preexisting dermatologic lesions in the direction of eosinophilia?

In any event, a new message has come to dermatologists. Patients with persisting erythema multiforme lesions (including migrating ones) demand study into the possibilities of Loeffler's syndrome. In the United States, animal parasites are not calculated to be demonstrated, but the experience in Palestine indicates that they are not a *sine qua non*.

The Syphiloid of Cats.—From the purely histologic viewpoint, the syphiloid of cats must be also regarded as one of the eosinophilic granulomas of the skin. Lever and also Lewis and Cormia supply adequate reasons for proving that it is neither etiologically nor clinically identical with the human cases described in the literature. However, to those who would insist that the concept of eosinophilic granuloma of the skin must comprehend a specific etiologic factor and a clinical picture that constitute an entity, the syphiloid of cats supplies the answer. It satisfies all the criteria for an entity—etiologic, clinical and histologic. By reason of priority, too, it would be the true eosinophilic granuloma of the skin. However, for practical purposes in human medicine, largely as the result of usage of the term, it appears to be advisable to include this lesser disease item within the larger and regard its eosinophilia as only an additional expression of the effects of one of the manifold etiologic agents (supposedly micro-organismal in this case) in the premises. Incidentally, an animal is at hand here for the experimental study of eosinophilic granuloma, and, inasmuch as several cases of eosinophilic granuloma of the skin have involved the lips, vulva or anus, the possibility of transmission from cats to human beings must not be forgotten. In fact, Pautrier stated in his discussion that Nanta and Gadrat's case was indistinguishable from the syphiloid of cats; the lesions were perianal and peribuccal.

SIGNIFICANCE AND ROLE OF LIPIDS

In my personally studied cases, only two opportunities were supplied for testing for the presence of fat in the skin. Singularly, it was demonstrated in both cases, and it is recommended that such tests be conducted routinely in future cases of eosinophilic granuloma of the skin and also that the fat content of the blood be determined. Lever, alone, raised this subject; he found a few lipid-laden histiocytes and foam cells in his sections. The significance of this toward Letterer-Siwe disease has been discussed sufficiently elsewhere, but extreme caution must be exercised in view of the presence of fat glands in the skin which might have become disintegrated. In the sections that I studied, though, there was not any evidence of such disintegration.

SUMMARY

The 10 European cases have been analyzed, the 20 cases occurring in Loeffler's syndrome and the syphiloid of cats have been discussed and sections have been examined by me in 9 American cases. They appear to fall into two groups pathologically, namely, the idiopathic and the symptomatic. A working classification is submitted on that basis, and it indicates also the widely divergent prognosis. Inasmuch as the disease is not an entity but only a histologic syndrome, "eosinophilic granulomas" is more fitting than "eosinophilic granuloma." "This is one of the eosinophilic granulomas of the skin" is a more proper statement when speaking of an individual case. The diagnosis can be made only histologically; sections are the first clue in diagnosis, but in view of the frequent plaquelike involvement of the face, it must be taken into account in the differential diagnosis of apparent sarcoid, leukemia, erythema elevatum diutinum and possibly lupus erythematosus. It is impossible to formulate blanket diagnostic formulas or prognoses to cover all cases of this disease.

Inasmuch as cutaneous manifestations appear in Loeffler's syndrome in the form of persistent erythema multiforme, it is in order (1) to determine whether sections of skin in this syndrome exhibit the features of eosinophilic granuloma and (2) to take note of the role of Loeffler's syndrome in dermatology. Eosinophilic granuloma of bone does not appear to be related to eosinophilic granuloma of the skin, but the demonstration of fat in cutaneous lesions opens the way for further inquiry through the avenue of Letterer-Siwe disease. The eosinophilic granuloma of cats (syphiloid) can be classified (histologically) among the eosinophilic granulomas of the skin at least temporarily.

The disease has appeared so abruptly in dermatology that attention should be paid to newer factors in the life of the population such as are calculated to induce eosinophilia (newer drugs and other agents).

In line with the ideas of Sulzberger [11] concerning histamine and allergy, the thesis is offered that the eosinophilic features are but additive to well known dermatologic entities such as erythema multiforme and Hodgkin's disease and that the eosinophilogenic factors may be responsible for obscuring and/or modifying the typical features of such entities. Of these factors, allergy stands in the forefront.

In the idiopathic group, eosinophilia of the blood (up to 72 per cent) is almost always present. The cellular infiltrate in the skin is far more polymorphous. The eosinophils vary in number at different stages of the disease, both in blood and in tissue, and one must be prepared for cases of eosinophilic granuloma of the skin *sine* eosinophilia.

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11. Sulzberger, M. B.: Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1944.

EOSINOPHILIC GRANULOMA

Theoretic and Practical Considerations Based on the Study of a Case

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A PATIENT with bizarre, recurrent, eosinophilic tumefactions of the skin has been under observation for the past three and one-half years. The clinical findings, in comparison to those noted in previous reports, are unique inasmuch as the individual lesions have been of relatively short duration with a tendency to spontaneous disappearance, are acutely inflammatory in nature and are completely insensitive to irradiation with roentgen rays.

As a background for discussion of this case, the pertinent literature will first be summarized. Following the presentation of the case, an attempt will be made to link up the various eosinophilic tumefactions into a logical pattern and to clarify the relationship between these lesions and eosinophilia in general.

SUMMARY OF ANALOGOUS CASES

The first case of cutaneous eosinophilic granuloma to be reported was that of Freund [1] in 1930. His patient had active pulmonary tuberculosis. For six years there were present livid red, semicircular infiltrations on the eyelids; hard, verrucoid and hyperpigmented nodules on the arms and legs, and a cordlike lesion on the right cheek and jaw. There was no significant adenopathy. Trichophytin test and serologic tests of the blood elicited negative reactions, while a blood eosinophilia of 22 per cent was present. Studies of biopsy specimens revealed a slight acanthosis and a vasodilatation and edema of the papillae. Throughout the cutis and extending to the subcutaneous tissues was a widespread, dense infiltrate, which had caused extensive destruction of connective tissue fibers, hair follicles and sebaceous glands. The infiltrate was predominantly eosinophilic, with, in addition, some lymphocytes,

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Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, June 10, 1946.

From the New York Hospital and the Department of Medicine (Dermatology), Cornell University Medical College.

1. Freund, E.: Su un caso di strari tumori cutanei in una tuberculosa, Dermosifilografo **5**:617 (Oct.) 1930.

monocytes, histiocytes, plasma cells, mast cells, giant cells and epithelioid cells. The blood vessels were the seat of extensive endarteritis with hyaline degeneration of the intima and adventitia. The lesions improved greatly after roentgen ray therapy, but the patient was lost from observation and the end result was not known. Freund stated the belief that the granuloma might represent an atypical form of mycosis fungoides or Hodgkin's disease.

Pasini's case,[2] properly labeled as eosinophilic granuloma, was the second example of the syndrome to be reported. The patient was a woman of 69 years, with long-standing nonulcerated tumefactions of the forehead, left side of the face and left mandibular region. The onset had been eight years before, with a nodule which slowly extended peripherally, with the formation eventually of an irregularly surfaced hemispheric area 5 by 7.5 cm. The lesions on the left side of the face began as three separate nodules, with gradual extension and coalescence over the side of the face and mandibular region. Slight pruritus was occasionally noted. The lesions were bluish red, were elastic to firm in consistency and presented considerable nodule-like irregularities of the surface. The peripheral borders were raised and indented, while the central areas were depressed and atrophic; ulceration never developed. There were no systemic symptoms or evidence of impaired general health. Physical examination, serologic tests of the blood for syphilis and roentgenograms of the skull, thorax, hands and feet gave normal results. The hemogram was normal with the exception of a white blood cell count of 11,600, the increase in cells presumably being due to eosinophils (41 per cent). Histopathologically, there were moderate atrophy of the epidermis and absence of interpapillary pegs. The principal abnormality was a compact dermal infiltrate extending from the subpapillary zone throughout the deeper cutis and at times to the subcutaneous fatty tissue. There was almost complete destruction of the normal elements of the connective tissue and the sweat glands. The infiltrate consisted of great numbers of eosinophils (either mononuclear or polymorphonuclear), with, in addition, considerable small and large lymphocytes, histiocytes and fibroblastic proliferation. There were a few plasma and mast cells but no giant cells. The smaller blood vessels were increased in number and were the seat of an extensive endarteritic thickening. Edema of the tissues was not present. Roentgenologic irradiation was given, with considerable improvement, but the end result was not stated.

Martinotti[3] recorded briefly 3 cases of "eosinophilic" granuloma, but of these only 1 seems to fit into the group of specific eosinophilic

2. Pasini, A.: Granuloma eosinofilo, Gior. ital. di dermat. e sif. **81**:1 (Feb.) 1940.

3. Martinotti, L.: Granuloma eosinophilum, Dermat. Wchnschr. **112**:25 (Jan. 11) 1941.

tumefactions. This patient was a soldier who had chronic, infiltrated and at times ulcerated plaques on the legs. On section, the infiltrate was found to be mainly eosinophilic, with some mast cells, plasma cells and fibroblastic proliferation. Cure was obtained by surgical excision.

Cerutti [4] has made the most recent report of this rare syndrome. His patient was a woman, aged 41, in whom during the preceding three months there had developed a nodular and noduloulcerative eruption. The lesions consisted of doughy to firm, reddish brown tumors, some with necrotic tops. The distribution was widespread, with a tendency to seborrheic localization; the scalp, hands and feet were spared. There was no lymphadenopathy except for a large cervical lymph node on the left side. A blood eosinophilia of 47 per cent was recorded. Histopathologic studies revealed (1) a lymphosarcomatous tumor of the cervical lymph nodes on the left side and (2) a granuloma, predominantly eosinophilic in type, involving the skin. In the cutaneous lesions a compact infiltrate involved the entire cutis. When the epidermis was not specifically invaded, there was an overlying acanthosis and spongiosis. In some areas, however, the epidermis was massively infiltrated with cellular elements from the granuloma in the cutis, and in these areas necrosis frequently supervened. The infiltrate in the cutis was massive and more or less completely replaced the normal structures. The cells were largely eosinophilic in type (both mononuclear and polymorphonuclear) and occurred both diffusely and in perivascular localizations. A few lymphocytes, epithelioid cells and histiocytes were also present. Cerutti noted that in peripheral zones histiocytes with acidophilic granules were present and expressed the opinion that these cells might be the precursors of tissue eosinophils. As in the cases of Freund and Pacini, the blood vessels were the seat of an extensive endarteritis and thickening, but the possible significance of this phenomenon was not discussed. The patient was given roentgen ray therapy, which effected a dramatic and permanent improvement in the eosinophilic tumors. The sarcoma, on the contrary, was unaffected, continued to spread and finally resulted in the death of the patient by its metastases. The progression of the sarcoma was not accompanied with a relapse of the cutaneous lesions, and Cerutti was of the opinion that the two diseases were unrelated.

OTHER EOSINOPHILIC TUMORS OF THE SKIN

The concept of a cutaneous eosinophilic granuloma as a well defined clinical entity has been complicated by the recent reports of cases by Pautrier,[5] Nanta and Gadrat,[6] Lapière [7] and Lefèvre and his associates.[8]

4. Cerutti, P.: Il granuloma eosinofilo, Dermatologica **85**:90, 1942.

The cases of Lefèvre and his co-workers and of Lapière will be discarded from further consideration as probable examples of lymphoblastoma of unknown type and Hodgkin's disease respectively. The patients described by Pautrier and by Nanta and Gadrat, while clinically distinct from the present case, had lesions which on histopathologic study showed a predominantly eosinophilic type of infiltrate, and for this reason they will be reviewed.

Pautrier's patient was a man aged 25 who had a perianal and rectal granuloma of one and a half years' duration. The lesions were verrucous and vegetating and extended from the primary location to the adjacent surface of the buttocks, the anal wall and for several centimeters along one side of the rectal mucosa. The patient had a partially treated syphilitic infection and had suffered previously from amebic dysentery. There was no clinical resemblance to lymphogranuloma venereum; however, the Frei test elicited a weakly positive reaction. Studies of a biopsy specimen revealed a decided verrucoid acanthosis and a dense infiltrate throughout the cutis. This infiltrate was composed of lymphocytes, plasma cells, small histiocytes and moderate numbers of eosinophils. Scattered polymorphonuclear cells and small zones of necrosis were noted.

The patient of Nanta and Gadrat was a man aged 21 who had diabetes insipidus, pleurisy and active pulmonary tuberculosis. Diffuse tumefactions developed on the lower gingiva and a vegetating granuloma in the perianal region and the distal part of the rectal mucosa. Histopathologic changes included a moderate acanthosis and a dense infiltrate throughout the cutis, predominantly eosinophilic, with, in addition, some histiocytes, monocytes, plasma cells and mast cells.

It is noteworthy for both patients that the striking endarteritis and subsequent vascular thickening noted in the patients of Freund, Pacini and Cerutti and in the case to be presented were conspicuous by their absence. The pronounced epidermal changes were probably indicative of a more "toxic" form of tissue reaction; moreover, blood eosinophilia was not a feature. It would seem that an entirely different type of pathologic tissue reaction was taking place, with such obvious etiologic

5. Pautrier, L. M.: Le granulome éosinophilique, Bull. Acad. de méd. de Roumanie **3**:432, 1938.

6. Nanta, A., and Gadrat, J.: Sur un granulome éosinophilique cutané, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **44**:1470 (July) 1937.

7. Lapière: Un cas de granulome éosinophilique, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **44**:1479 (July) 1937.

8. Lefèvre, P.; Coirre, and Lévy-Coblentz, G.: Granulomatose cutanée à évolution fébrile avec éosinophilie sanguine à 46% sans determinations ganglionnaires, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **44**: 1604 (July) 1937.

possibilities as cutaneous amebiasis, tuberculosis and lymphogranuloma venereum to be strongly considered.

It would seem that the cases both of Pautrier and of Nanta and Gadrat bore superficial resemblances to the so-called syphiloid of the cat, recently described by Henry and Bory.[9] However, in this ill defined entity, the sites of involvement are different. Chancriform lesions are present on the lip and hypertrophic plaques in the inguinocrural and perianal regions. Moreover, a satellite or distal lymphadenitis is often a prominent feature. Lastly, the cellular infiltrate, while somewhat similar to that seen in eosinophilic granuloma, is unaccompanied with significant changes in the blood vessels.

REPORT OF A CASE

M. R., a Jewish-American man of 47, was first seen three and one-half years ago because of recurrent, moderately pruritic tumefactions involving the trunk and extremities. He was presented at the Manhattan Dermatologic Society in October 1942 (A Case for Diagnosis [Erythema Nodosum?], ARCH. DERMAT. & SYPH. **48**:436 [Oct.] 1943) and at the New York Academy of Medicine, Section on Dermatology and Syphilis, in May 1943 (A Case for Diagnosis [Eosinophilic Granuloma?] ARCH. DERMAT. & SYPH. **49**:375 [May] 1944).

The family history was unremarkable, there being no constitutional or allergic diseases and no serious infections. The patient has shown some increased susceptibility to infections. Because of recurrent tonsillitis, tonsillectomies were performed at the ages of 12, 13, 14 and 25. Five abscessed teeth were extracted between the ages of 19 and 30; at the latter time fourteen additional teeth, all with abscesses, were removed. He then began to experience severe headaches and during the ten years intervening up to the onset of the present trouble took large doses of acetylsalcylic acid and other coal tar derivatives. A chronic dermatophytosis of the soles and interdigital areas of the feet has been present for at least seven years. Vesiculation or other acute inflammatory changes have never occurred, and dermatophytid has not ensued. There was, moreover, no increase in the severity of the dermatophytosis just prior to the onset of the chief complaint.

The present cutaneous disease began six years ago on the inner aspect of the left thigh, as a small, firm, pinkish papule. Independent satellite lesions were soon noted; all areas enlarged peripherally and formed a large, deep, soft, pendulous sac, with evidence of edema shown by a pigskin-like surface. The color was initially pinkish red, became a darker red after seven to ten days and then gradually faded out as the lesions disappeared during the following two weeks. Involution has always been followed by a moderate degree of residual hyperpigmentation. Four of these tumefactions made their appearance on the thighs during the first four months of the disease, following which there was a six month period of freedom. Recurrences were then noted, this time involving both the arms and the thighs. The evolution of the lesions, while similar in pattern, became much slower, and nine to ten weeks were required for the complete cycle. The lesions were initially gyrate in configuration, later becoming deep, hard, solid plaques which

9. Henry, A., and Bory, L.: La syphiloïde du chat (granulome éosinophilique), Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **44**:1486 (July) 1937.

eventually softened and cleared from within outward. Furthermore, during the height of the multiple plaque formation, the entire lower extremities became swollen to one-half greater than normal size. During the next two years, the

Fig. 1.—Lesions of eosinophilic granuloma at various stages of evolution. *A*, early lesions. *B*, plaquelike tumefaction due to peripheral enlargement. *C*, massive edema at height of process and *D*, spreading process with solitary and plaquelike lesions.

body became increasingly involved by the process and even the soles were affected. The scalp, face and neck have been consistently free. The plaquelike character of the lesions has continued to date; the diffuse swelling, on the contrary, abated after another year and has been absent in the last three years to date. Lesions have been absent only for brief periods during the past five years, but there has been a gradual decrease in severity of attacks in the last two years. Ulceration has never occurred.

The attacks are invariably preceded by severe burning urination, increased frequency and polyuria. The tumefactions are accompanied throughout their course with a moderate pruritus, which is difficult to relieve by either local or systemic therapy. Local trauma has apparently resulted in the development of new lesions, but only in periods when lesions are spontaneously occurring. Treatment of the

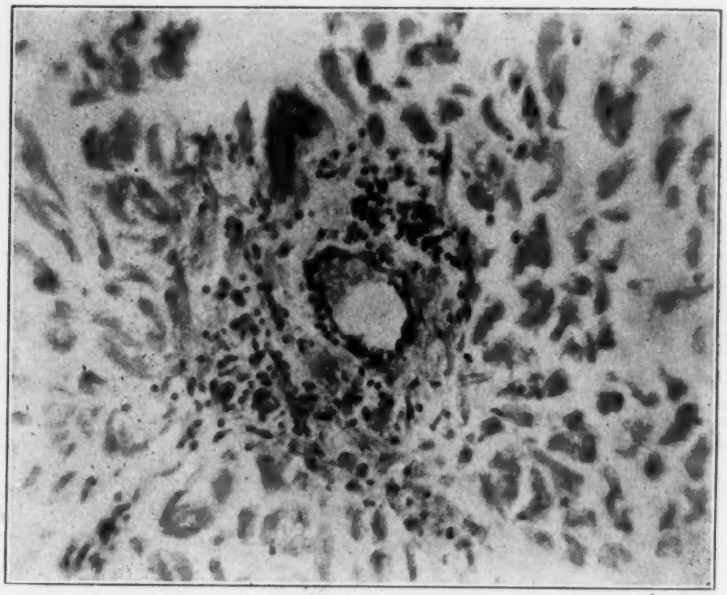

Fig. 2.—Early lesion, showing beginning vascular and perivascular changes.

accompanying dermatophytosis with ointment of benzoic and salicylic acid during periods of remission has resulted in a new severe attack on three occasions. Increase in size is thought to result from aggravation from nervous tension, but the attacks are never initiated in this fashion.

Extensive laboratory investigations were made three and one-half years before this paper was written and have been made at various intervals to date. Significant positive results were as follows: (1) isolation of Trichophyton purpureum from the dermatophytosis of the feet; (2) strongly positive immediate and delayed trichophytin reaction, with a central wheal of 2 cm. and a surrounding erythema of 4 to 5 cm.: (3) blood eosinophilia varying from 5 to 13 per cent, and (4) bone marrow eosinophilia of 15 per cent. Significant negative results included normal findings in urinalyses, roentgenograms of the chest, blood cultures, sedimentation rate, tuberculin test, prostatic culture and an extensive series of intradermal tests with pollens, dusts, feathers, various animal extracts, foods, orris root, pyrethrum.

flaxseed, silk, tobacco, trees, timothy and ragweed. Examination of the stool did not reveal parasites, and cultures of several biopsy specimens of the skin were negative for pathogenic bacteria and fungi. The Kline and Kahn tests of the blood elicited negative reactions.

During the period of observation some twenty biopsy specimens were examined. Specimens were taken from lesions at various stages in their evolution, and it was possible therefore to reconstruct to some degree the sequence and pattern of the pathologic changes. The significant abnormalities occurred only in the cutis. The epidermal changes were purely secondary in nature; in early lesions the epidermis was normal; later a slight acanthosis was variably present, while lesions which had undergone involution contained a moderate increase in melanin pigmentation in the basal layer.

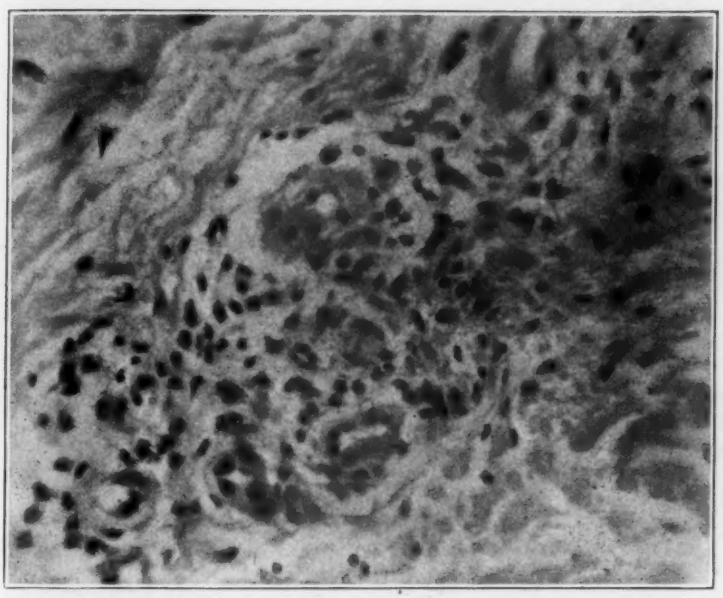

Fig. 3.—More pronounced early lesion, with endarteritis, dilatation of the lymphatic vessels and pleomorphic infiltrate.

The earliest demonstrable pathologic lesion was a mild dilatation of the smaller blood vessels of the subpapillary zone and the mid cutis, with some swelling of the endothelial cells and adherence of blood-borne leukocytes to the lumens. These dilated vessels were surrounded by a sparse infiltrate composed mainly of small lymphocytes and a few histiocytes.

As the evolution of the lesions continued, beginning endarteritis and thickening of the small blood vessels could be noted; the perivascular infiltrate became more pronounced and more pleomorphic in character, with lymphocytes, histiocytes, plasma cells and a few mononuclear eosinophils. The perivascular lymphatic vessels showed considerable engorgement.

In a moderately advanced lesion, the infiltrate became more compact and could be noted throughout the middle and deeper portions of the cutis. It still showed a tendency to a perivascular distribution with a dense encroachment on blood

vessels that were the seat of decided endarteritis and thickening. It also occurred around sweat ducts, hair follicles and sebaceous glands. While the pleomorphic type of infiltrate remained, increasing numbers of mononuclear and polymorphonuclear eosinophils could be observed. Moderate edema of the tissue had now supervened.

In a fully developed lesion the infiltrate was almost solidly present throughout the mid portion and deeper portions of the cutis, while in some sections it had even invaded the subcutaneous adipose tissue.

Much of the normal connective tissue was replaced by the dense masses of cells, while the entire section showed a rather decided edema. The blood vessels were extensively thickened, in some instances with diminished lumens and in others with complete obliteration of the lumen. The infiltrate, while retaining

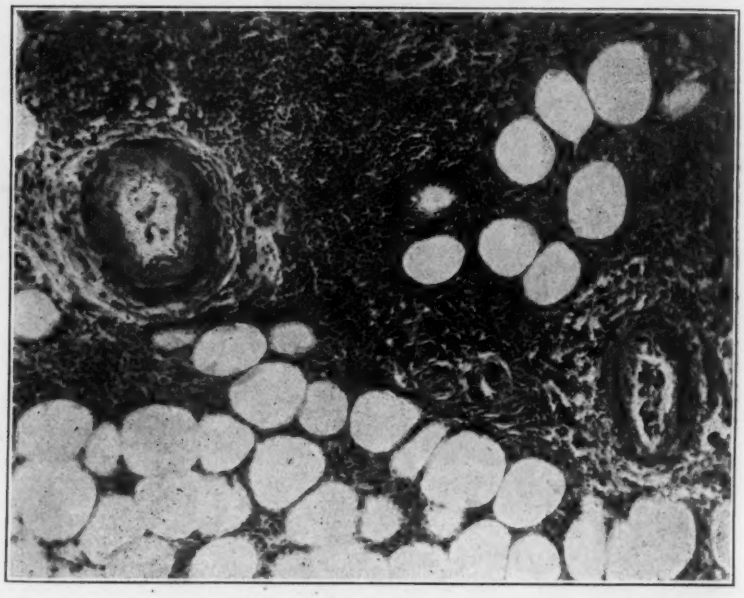

Fig. 4.—The fully developed lesion shows extensive endarteritis and massive eosinophilic invasion of the deep cutis.

its polymorphous character, contained a great increase in percentage of mononuclear and polymorphonuclear eosinophils. The eosinophils were seen throughout the granuloma. However, they tended to be concentrated along the outer walls of the blood vessels. In some areas eosinophils were noted lying free along the collagen fibers, and eosinophilic granules could be seen extracellularly in the tissue.

As the lesions receded, the infiltrate became less eosinophilic in character and lymphoblasts, histiocytes and small leukocytes were more numerous. A striking feature was observed in a biopsy specimen taken two years after clinical involution of the lesion had occurred. In this section eosinophils, histiocytes and plasma cells were absent, and only a sparse perivascular infiltrate of small lymphocytes was present. The blood vessels, however, still showed a considerable amount of endarteritic thickening of a regressive type. Corresponding to the residual hyper-

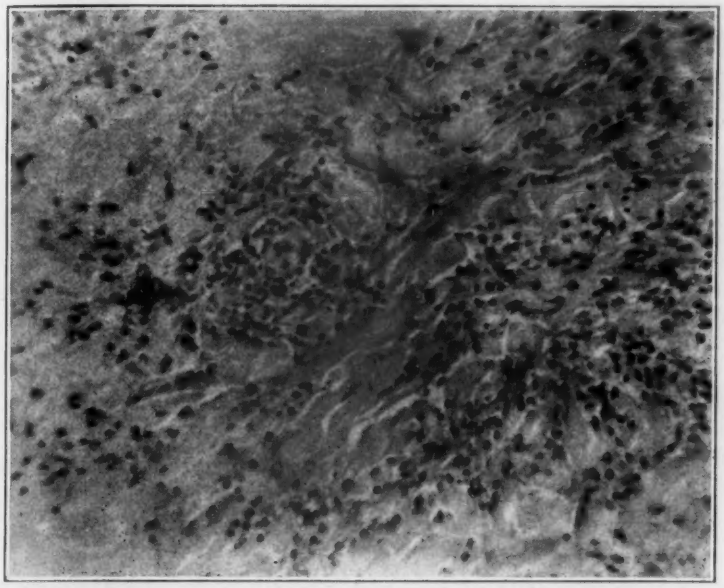

Fig. 5.—Advanced lesion, showing eosinophilic infiltrate occurring perivascularly and along collagen fibers.

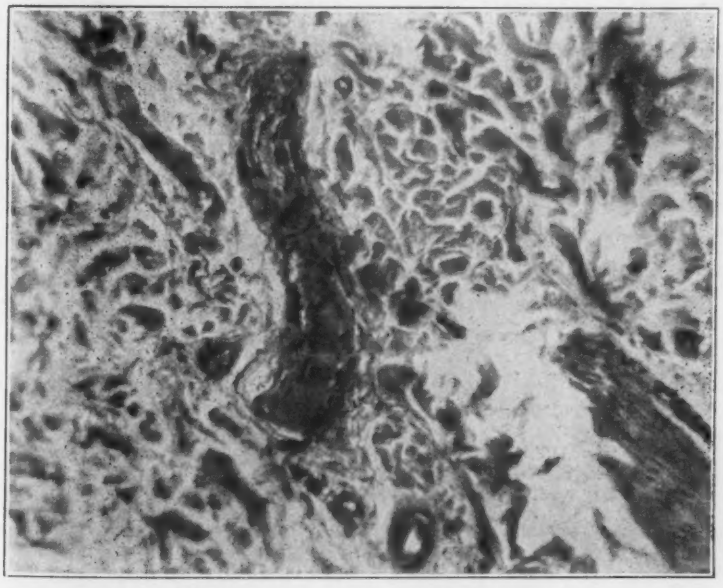

Fig. 6.—Lesions which have undergone involution, showing hyperpigmentation, residual endarteritis and perivascular infiltration.

pigmentation noted clinically, appreciable amounts of melanin were present in the deeper layers of the epidermis.

The clinical progress of the lesions was but slightly modified by therapy. Roentgen irradiation was entirely without effect, while various topical remedies were of but minor palliative value. Two courses of potassium iodide by mouth were administered. There was no improvement during the first course, but the second course, which continued for eight months, with the eventual establishment of a daily dose of 280 grains (15.8 Gm.), effected a 30 per cent amelioration in the severity of the lesions. It is interesting also that an injection of trichophytin two years previous to the writing of this paper was followed by a clinical exacerbation. Recently, eight intradermal injections of trichophytin and histamine at weekly intervals were administered. This treatment resulted in no demonstrable improvement of the disease; on the contrary, the customary involution of the lesions was delayed, and finally a striking exacerbation occurred, so the therapy was discontinued.

EOSINOPHILIC GRANULOMAS IN OTHER BODY STRUCTURES

Other tissues and organs may be the sites of granulomatous tumors somewhat comparable to those seen in the skin. Specifically, the bones,[10] the lungs,[11] and the reticuloendothelial system [12] have been reported to be involved.

The bone lesions, first reported by Mignon,[10] may be solitary or multiple, affecting frequently the skull and occurring commonly in childhood and adolescence. The tumefactions are reported to follow trauma frequently. Specific allergic factors have not been determined. Pathologically, the granulomas are composed of compact masses of large histiocytes associated with mature and immature eosinophils. Polymorphonuclear, plasma and giant cells are occasionally seen. As the disease progresses, foam cells and an increased amount of lipid may be present. Replacement of connective tissue finally makes way for transformation back to bone.[13] Roentgenographically and at times pathologically, the lesions of eosinophilic granuloma of bone are indistinguishable from Hand-Schüller-Christian disease involving bone.[14] Frequently, there is an associated blood eosinophilia of 5 to 10 per cent. The lesions may disappear spontaneously or be cured by roentgen therapy or surgical excision.

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10. Mignon, F.: Ein Granulationstumor des Stirrbeins, Fortschr. a.d. Geb. d. Röntgenstrahlen **42**:749 (Dec.) 1930.

11. Löffler, W.: Die flüchtigen Lungeninfiltrate mit Eosinophilie, Schweiz. med. Wchnschr. **66**:1069 (Nov. 7) 1936.

12. Jaffe, H., and Lichtenstein, L.: Eosinophilic Granuloma of Bone, Arch. Path. **37**:99 (Feb.) 1944.

13. Green, W., and Farber, S.: Eosinophilic or Solitary Granuloma of Bone, J. Bone & Joint Surg. **24**:499 (July) 1942.

14. Mallory, T.: Medical Progress. Pathology: Diseases of Bone, New England J. Med. **227**:955 (Dec. 17) 1942.

The pulmonary syndrome, first described by Löffler,[15] occurs as transient pulmonary infiltrations, often recurrent, accompanied with cough, mild fever and symptoms of asthma. There is a mild leukocytosis with a blood eosinophilia of 10 to 50 per cent and a high bone marrow eosinophilia.[16] The disease is reputedly not fatal, so that it is interesting and noteworthy that von Meyenburg[16] described the pathologic anatomy of the pulmonary lesions in 3 subjects, all of whom died accidentally in Nazi Germany in 1942. According to von Meyenburg the lesions consist of an exudative inflammatory process accompanied with an infiltrate composed largely of eosinophils. A few lymphocytes, polymorphonuclear cells, plasma cells and giant cells are variably present and often perivascular in location. In some districts areas of thrombophlebitis and of necrosis have been found, but endarteritis was not described.

Specific allergenic factors such as amebas, intestinal worms, plants and pollens have been identified as causative agents in several cases,[17] and the elimination of these agents has resulted in permanent cure.

In cases reported to involve the reticuloendothelial system, the evidence is less convincing. In the syndrome described by Letterer[18] and Siwe[19] there develops during the first year of life a widespread histiocytosis involving the reticuloendothelial system, in which the bone marrow, liver, spleen, lymph nodes, alimentary tract, thymus and skin may be affected. The disease is invariably fatal when it develops in early infancy and becomes more benign, with chronicity the rule, when the onset is after the age of 2. Histologically the tumor cells consist of histiocytes, lymphocytes, plasma cells and eosinophils. At times the eosinophils may predominate. It has been reported that Hand-Schüller-Christian disease may supervene after a patient has reached the age of 2, becoming more typical by the fourth year of life.[14] Because of this reported transition to a probably unrelated disease and because of the absence of any significant allergic factors, the resemblance of the Letterer-Siwe syndrome to eosinophilic granuloma may be more apparent than real.

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15. Löffler, W.: (A) Zur Differential-Diagnose der Lungeninfiltrierungen; (B) Ueber flüchtige Succedan-Infiltrate mit Eosinophilie, Beitr. z. Klin. d. Tuberk. **79**:338, 1932.

16. von Meyenburg, H.: Das eosinophile Lungeninfiltrat: Pathologische Anatomie und Pathogenese, Schweiz. med. Wchnschr. **72**:809 (July 25) 1942.

17. Jones, S., and Souders, C.: Eosinophilic Infiltration of the Lungs (Löffler's Syndrome), New England J. Med. **231**:356 (Sept. 7) 1944.

18. Letterer, E.: Aleukämische Retikulose, Frankfurt. Ztschr. f. Path. **30**: 377, 1924.

19. Siwe, S.: Die Reticuloendotheliose—ein neues Krankheitsbild unter den Hepatosplenomegalien, Ztschr. f. Kinderh. **55**:212, 1933.

COMPARABLE TISSUE REACTIONS

A critical analysis of repeated biopsy material suggests that the fundamental evolutionary features of the disease are: (1) involvement of the smaller blood vessels of the skin, with dilatation and adherence of leukocytes to their endothelial surface, (2) beginning endarteritis and thickening of the vessels, with dilatation of the perivascular lymph spaces and an infiltrate which is at first lymphocytic but later becomes predominantly eosinophilic, (3) development of pleomorphism of the infiltrate, (4) more diffuse distribution of the eosinophilic infiltration and widespread edema, (5) gradual resorption of the infiltration and (6) the end stage of residual endarteritis and hyperpigmentation.

In the cases reported by Freund, Pasini and Cerutti, the histopathologic features were essentially similar, although the evolution of the pathologic lesions was not clearly defined.

In the cases described by Pautrier and by Nanta and Gadrat, the infiltrate was comparable but there was no evidence of a primary disturbance of the blood vessels.

The infiltrate noted in the osseous and pulmonary lesions is of comparable nature, but the absence of stated vascular changes prohibits any further analogy.

There would appear to be a striking similarity between the pathologic findings of periarteritis nodosa and eosinophilic granuloma of the skin, for in both diseases there is an initial involvement of the walls of the blood vessels and a subsequent pleomorphic infiltration in the perivascular tissues. In the first-named disease there is a more profound reaction in the arteries, with necrosis of the medium, obstruction and thrombosis of the lumen and subsequent infarction. The infiltrate, while similar to eosinophilic granuloma, is more localized. Furthermore, the disease may be widespread throughout the body. Recent observations [20] have suggested that in many, if not the majority of, instances the disease may be self limited, healing with residual fibrosis.

DELELOPMENT OF EOSINOPHILIA: EXPERIMENTAL OBSERVATIONS BY OTHERS

From a consideration of experimental studies regarding the behavior and development of eosinophils, these cells have been shown to appear in the blood and/or tissues after exposure to the following substances: (1) injection in animals of foreign protein in the form of specific or

20. Rich, A.: The Role of Hypersensitivity in Periarteritis Nodosa as Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy, Bull. Johns Hopkins Hosp. **71**:123 (Sept.) 1942.

nonspecific antigens;[21] (2) injection of suspension in isotonic solution of sodium chloride of ground ascaris[22] in guinea pigs; (3) intramuscular injections of foreign proteins in human beings;[23] (4) sensitization by haptene antigens (phenylethylhydantoin or sulfonamide drugs[24]) and (5) in tissue cultures in presence of circulating antibodies.[25]

The consensus is that the eosinophils are produced only in the bone marrow,[26] as first postulated by Ehrlich,[27] although some authors[28] hold that they may arise in local tissues as well.

DISEASES IN WHICH EOSINOPHILIA IS A FEATURE

Eosinophilia is a feature in the following diseases: (1) pruriginous diseases of the skin with repeated excoriations (dermatitis herpetiformis, lymphoblastomas such as mycosis fungoides, prurigo and atopic eczema[28]); (2) diseases of the skin with excessive destruction of tissue (pemphigus)[28]; (3) blood dyscrasias (Hodgkin's disease and eosinophilic leukemia, myelogenous leukemia and familial eosinophilia[26]); (4) intestinal parasites and trichinosis[26]; (5) allergic diseases (urticaria and asthma); (6) diseases probably of allergic nature (periarteritis nodosa[29] and Löffler's syndrome[11]); (7) drug reactions, including those due to phenylethylhydantoin, benzene and digitalis,[26] and (8) miscellaneous diseases and states (splenomegaly, splenectomy, polymyositis, ingestion of raw liver, ultraviolet irradiation and roentgenologic irradiation[30]).

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21. (*a*) Schlecht, H., and Schwenker, G.: Ueber locale Eosinophilie in den Bronchien und der Lunge beim anaphylaktischen Meerschweinchen, Arch. f. exper. Path. u. Pharmakol. **68**:163, 1912. (*b*) Biggert, J.: Some Observations on Eosinophile Cell, J. Path. & Bact. **35**:799 (Sept.) 1932.

22. Herrick, W.: Experimental Eosinophilia with an Extract of an Animal Parasite: Its Relation to Anaphylaxis and Certain Clinical Problems, Arch. Int. Med. **11**:165 (Feb.) 1913.

23. (*a*) Biggart.[21b] (*b*) Peshkin, M. M., and Messer, W.: Asthma in Children: XII. Influence of Specific and Nonspecific Treatment on the Differential Leukocyte Count, with Special Reference to the Eosinophils, Am. J. Dis. Child. **50**:1374 (Dec.) 1935.

24. Landsteiner, K.: Serological and Allergic Reactions with Simple Chemical Compounds, New England J. Med. **215**:1199 (Dec. 24) 1936. Rich.[20]

25. Haughton, B., cited by Kirk.[26]

26. Kirk, R. C.: The Causes of Eosinophilia, Internat. Clin. **1**:219 (March) 1942.

27. Ehrlich, P.: Methodologische Beiträge zur Physiologie und Pathologie der verschiedenen Formen der Leukocyten, Ztschr. f. klin. Med. **1**:553, 1879-1880.

28. Burkhart, R., and Montgomery, H.: Dermatologic Significance of Tissue Eosinophilia, Arch. Dermat. & Syph. **49**:19 (Jan.) 1944.

29. Lebowich, J., and Hunt, H.: Eosinophilia: Diagnostic Significance in Periarteritis Nodosa, Am. J. Clin. Path. **10**:642 (Sept.) 1940.

(Footnotes continued on next page)

FUNCTION OF THE EOSINOPHILS

At the present time, the exact function is unknown. From the previously mentioned experimental work and listed diseases in which eosinophilia is noted in human beings, it would seem that eosinophilia develops as a result of destruction of body tissues or as a reaction to some protein or haptene antigen. Weinberg and Seguin have shown that eosinophils are phagocytic for bacteria, trichinella and peptone.[31] In addition, Code [32] has demonstrated that the histamine content of the blood is high in patients with eosinophilia. This raises the question whether eosinophilia and increased blood histamine are adventitious findings produced by a single factor or whether the eosinophils appear as the result of stimulation by histamine. The suggestion has been made that the eosinophilic granules have a high concentration of histamine, possibly as a protective mechanism.[26]

SPECIFIC ETIOLOGIC CONSIDERATIONS

Examination of the reports of cases of previous examples of eosinophilic granuloma does not reveal a single instance in which a cause was determined. While the cause in the present case has not been finally proved, the following findings are of interest:

1. There was repeated demonstration of a T. purpureum infection of the feet.

2. Both immediate and delayed cutaneous hypersensitivity to trichophytin was present.

3. Vigorous treatment of the dermatophytosis resulted in definite exacerbation of the eosinophilic granulomas on three occasions.

4. During a series of intracutaneous trichophytin injections, there was a pronounced delay in the involution of the existing granulomas in comparison with previous attacks.

5. A widespread exacerbation of the disease developed two hours following an injection of trichophytin.

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30. Goldsmith, W. N.: Recent Advances in Dermatology, Philadelphia, P. Blakiston's Son & Co., 1936, p. 440. Minot, G., and Spurling, R.: Effect on Blood of Irradiation, Especially Short Wave Length Roentgen-Ray Therapy, Am. J. M. Sc. **168**:215 (Aug.) 1924. Kirk.[26]

31. Weinberg, M., and Seguin, P.: Recherches biologiques sur l'eosinophilie; propriétés phagocytaires et absorption du produits vermineux, Ann. Inst. Pasteur **29**:323, 1915.

32. (*a*) Code, C.: Source in Blood of Histamine-like Constituent, J. Physiol. **90**:349 (Aug. 17) 1937. (*b*) Code, C., and Hester, H.: Blood Histamine During Anaphylactic Shock in Horse and Calf, Am. J. Physiol. **127**:71 (Aug.) 1939. (*c*) Code, C.: Histamine Content of Blood of Guinea Pigs and Dogs During Anaphylactic Shock, ibid. **127**:78 (Aug.) 1939.

6. Typical eosinophilic granulomas appeared at the site of several of the trichophytin injections, whereas none appeared at control sites.

7. There was an absence of any other explanation for the disease.

8. Intensive and prolonged internal iodide therapy resulted in moderate clinical improvement.

SUMMARY

1. A patient with frequently recurring pruritic edematous tumefactions of the skin has been studied for the past three and one-half years.

2. The disease was characterized pathologically by endarteritis, followed by a predominantly eosinophilic infiltration.

3. Evidence is submitted suggesting a relationship with a coexisting fungous infection of the feet (T. purpureum).

4. Reports of cases of eosinophilic granuloma of the skin, bones, lungs and reticuloendothelial system have been reviewed.

5. The theories concerning the development and function of eosinophils have been considered.

6. Since the initial and fundamental pathologic change of the skin is apparently in the blood vessels, the name eosinophilic perivasculitis would seem preferable to eosinophilic granuloma.

66 East Sixty-Sixth Street.

ABSTRACT OF DISCUSSION

DR. UDO J. WILE, Ann Arbor, Mich.—I should like to report and to demonstrate another case of eosinophilic granuloma which was recently presented at a meeting of the Central States Dermatological Society and which is now in press to be reported in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY. This case is particularly interesting because it has the findings of both the Letterer-Siwe syndrome with lesions in the bone and cutaneous lesions at the same time, with a remarkable spontaneous recovery of the bone lesions and recovery of all the cutaneous lesions under irradiation.

This is a child of 16 months in whom at the age of 8 months there developed ulcerative and fungating lesions in the groin and on the tongue and on the buccal mucosa. The biopsies were initially performed. My associates and I had no suspicion of any bony lesions at this time. Under the microscope, the picture was one of a reticular structure with large numbers of histiocytes and eosinophils, and subsequent examination and reference of the slides to Dr. Hamilton Montgomery established a probable diagnosis of eosinophilic granuloma.

Then we had the roentgenologic demonstration of the bony lesions. These lesions were the ulcerative and fungating type of the skin. They were around the genitalia and in the axilla. There were lesions in the mouth and on the tongue and also a large lesion on the abdomen. I want to call attention here to the remarkable changes in the bones. There is a lesion which could readily be confused with a malignant growth, sarcoidosis and sporotrichosis.

Lesions in the skull and a second lesion scattered around the ribs are much like those of a malignant growth.

This was the microscopic picture, essentially—not altogether—the same as those shown by our president, but more like some of those shown by Dr. Weidman but not very similar to those in Dr. Lewis' case. There were large numbers of the eosinophilic cells throughout, and originally we felt that this was probably a reticuloendothelioma, for lack of a better diagnosis.

Under mild irradiation all the cutaneous lesions underwent complete resolution, and during the period of observation the lesion in the bone also completely disappeared; whether the latter disappeared under the influence of roentgen rays or whether they disappeared spontaneously is open to question. At no time were eosinophils found in the blood.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I was much interested in the excellent papers by Dr. Weidman and by Dr. Lewis and Dr. Cormia.

Dr. Burkhart and I wrote on tissue eosinophilia (ARCH. DERMAT. & SYPH. **49**:19-26 [Jan.] 1944), but we missed the articles on eosinophilic granuloma of bone written by the general pathologists. Dr. A. C. Broders called my attention to this condition some months ago, and I believe that there is no question that Dr. Curtis' case to which Dr. Wile referred in this discussion is one of that disease with cutaneous manifestations.

Dr. Walter Lever is reporting a case of eosinophilic granuloma of the skin in which there were foam cells and which he suggests is related to eosinophilic granuloma of the bone. The latter condition belongs with Hand-Schüller-Christian disease. The general manifestations are not so severe as those of Letterer-Siwe disease. Farber, I believe, would withdraw these conditions from disorders of lipid metabolism, regarding any deposits of lipids as secondary and not primary factors. Yet, there are many cases of Hand-Schüller-Christian disease on record, including those reported by Dr. Weidman and his associates with concomitant lesions of xanthoma disseminatum on the skin.

One of Dr. Weidman's cases of eosinophilic granuloma of the skin, as he stated, was strongly suggestive of Hodgkin's disease. In Dr. Lewis' case of eosinophilic granuloma, the question was raised of possible periarteritis nodosa. Whereas there was some thickening of the endothelium as shown in the slides that were projected, a typical one-sided involvement of all the muscle layers was not apparent. Rich, of Baltimore, has advocated an allergic basis for periarteritis nodosa. Eosinophilia of the blood or tissue, however, is not necessarily indicative of an allergic basis. Among other eosinophilic infiltrations of the skin one might include pemphigus vegetans, in which decided acanthosis together with microabscesses filled with eosinophils makes for a diagnostic picture.

DR. CARROLL S. WRIGHT, Philadelphia: I want to say a word about the treatment of the patient that Dr. Weidman has mentioned. This woman came with a lesion that did not look unlike a chancre. She had been studied by two other dermatologists with that idea, who had advocated Wassermann tests, which elicited negative reactions, but no one had performed a biopsy. The lesion was about the size of a dime, so while I was taking a section for biopsy I thought that I would desiccate it. Healing was complete in two or three weeks.

She returned in March with an almost identical lesion, and, because of my experience with the other lesion, I again applied desiccation, with complete healing.

This would be applicable in small ulcerated lesions only, but I thought that it might be worth while to mention in case any dermatologists saw a similar case.

DR. EARL W. NETHERTON, Cleveland: After hearing these two excellent presentations, and particularly Dr. Weidman's presentation, there seems to be con-

siderable doubt in my mind as to whether the case that I presented before the society last year as discoid lupus erythematosus with superimposed xanthomatous infiltration might not have been, in reality, an eosinophilic granuloma.

A few weeks ago Dr. Weidman corresponded with me, asking if we couldn't get this patient back. Since she lived out of the city, it was difficult to have her return. She did, however, return about two weeks ago, and the lesions on her face showed decided regression, leaving slight, thin, atrophic scarring. The xanthosis had decreased but had not completely disappeared. The erythematous phase of the eruption had almost entirely cleared up.

After hearing from Dr. Weidman, I reviewed the sections again. Unfortunately, biopsy specimens were not obtained from the early portion of the lesion. However, I obtained two biopsy specimens, one in the strictly xanthomatous process and one taken where the lesion was erythematous but still showing the yellowish discoloration. In none of these sections were my associates and I able to find eosinophils. The eosinophilia at the present time is 5 per cent. She had a leukocyte count of 5,500.

I might state also that after my last observation she received bismarsen. How much this influenced the regression of the lesions, I am unable to state. However, I feel that my case may have been one of eosinophilic granuloma. However, we did not see the patient at a time when eosinophils could de demonstrated. This possibility will remain open to dispute until other similar cases have been observed.

Also, I should like to report briefly the case of a 3 month old child that had an eosinophilic granuloma of the groin with lesions involving the right scapula, the fifth rib and the eleventh dorsal vertebra. This child was born, so we are told by the family physician, with a papular eruption. The lesions when we saw the child were few, but they were uniformly pea sized and smooth, slightly scaly, dull red papules. The mother of the patient would not permit investigation at the time, stating that she would return later. She did return three weeks later, and the eruption had disappeared leaving varioliform scarring. The lesions in the bones at the present time are showing regression with irradiation.

Dr. George M. Lewis, New York: Recently our patient had a rather severe exacerbation, and for want of something better to do, we gave him Benadryl; there was an immediate and striking response in the relief of itching. There was no change at all in the lesions themselves.

In spite of what Dr. Montgomery said in his discussion, it would seem that the work of Rich and others has shown that periarteritis nodosa is not the invariably fatal disease that it was once considered, so that it may not be too far out of line to consider that some of these cases of eosinophilic granulomas border on the domain of that disease.

EOSINOPHILIC GRANULOMA OF THE SKIN

Its Relation to Erythema Elevatum Diutinum and Eosinophilic Granuloma of the Bone; Report of a Case

WALTER F. LEVER, M.D.
BOSTON

THE CASE to be presented has many clinical and histologic features in common with erythema elevatum diutinum and with eosinophilic granuloma of the skin. Eosinophilic granuloma has been described as a disease of the skin and of the bone, but whether the two diseases are related is not yet certain.

In the following report the clinical and histologic appearance of erythema elevatum diutinum, eosinophilic granuloma of the skin and eosinophilic granuloma of the bone will be reviewed and the possibility of a relationship discussed.

REPORT OF A CASE

A 47 year old woman first noticed in 1935 a small purple patch in the left malar region. In 1939 two additional lesions appeared, one on the right cheek and one just below the first lesion on the left cheek. All three patches gradually increased in size, and by 1942 the two on the left cheek had united. The lesions were not tender, and only when the patient was emotionally disturbed did the larger one on the left cheek swell slightly and throb. The patient stated that her general health had been good throughout these years.

Examination in 1945 revealed two purple lesions, one on each cheek (fig. 1 *A*). The larger lesion on the left measured 5.5 by 5 cm., the smaller on the right, 2.3 by 2.8 cm. Both had sharply defined, irregular borders. The epidermis appeared normal except that the follicular openings were more prominent than is usual. The lesion on the left cheek (fig. 1 *B*) presented diffuse infiltration at the upper and medial margins and irregular, nodular infiltration throughout. The infiltrate felt soft, almost elastic to the touch. The lesion on the right cheek was not infiltrated. The larger lesion showed, in areas in which the infiltration was more pronounced, an admixture of a yellowish brown hue. Aside from the cutaneous lesions, the physical examination revealed no abnormalities.

Treatment.—The lesions were treated by roentgen rays between December 1941 and April 1943. A total of 2,200 r were administered to the small lesion on the right cheek and 1,600 r to the large lesion on the left. No effect was noted.

Laboratory Data.—The results of urinalysis and several blood cell and differential counts were normal. The basal metabolic rate was —11 per cent. The serum cholesterol content measured 278 mg., nonprotein nitrogen 25 mg. and protein 8.2 Gm. per hundred cubic centimeters. Roentgenograms of the entire skeleton disclosed normal structure.

From the Departments of Dermatology and Pathology, Massachusetts General Hospital.

Fig. 1.—*A*, appearance of the lesions in 1945; *B*, close-up of the larger lesion. Dilated pilosebaceous follicles are visible. (The small white area near the lower border of the lesion is a scar left by taking a specimen for biopsy.)

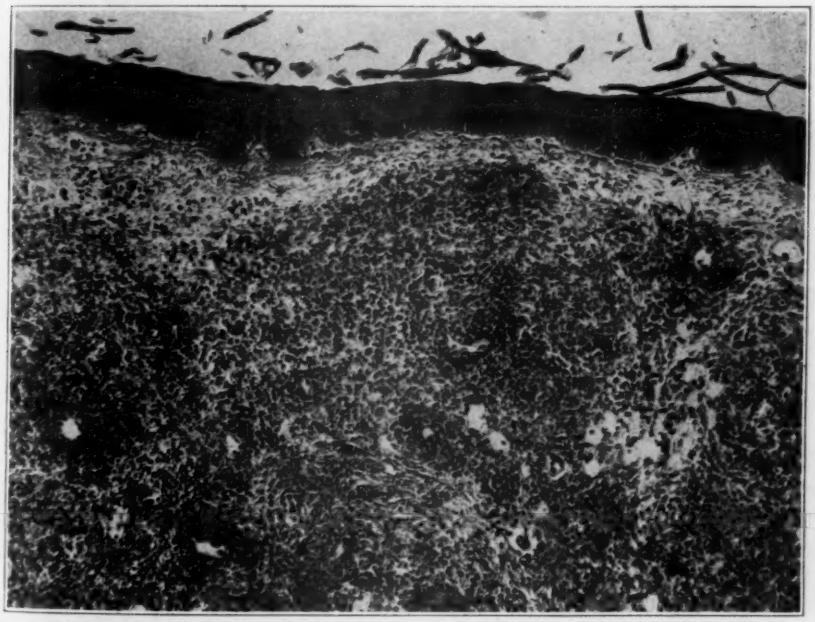

Fig. 2.—Section taken in 1942. Phloxine–methylene blue stain. The infiltrate is diffuse; it is densest around the capillaries. Eosinophils and neutrophils predominate. On the right side, groups of foam cells are present; × 90.

Bacteriologic Studies.—After a thorough cleansing of the skin with soap and alcohol, a piece of skin was removed, with the aid of a 6 mm. biopsy punch, from an infiltrated area of the larger lesion. The specimen was divided into an upper portion, including the epidermis, and a lower portion. Aerobic and anaerobic

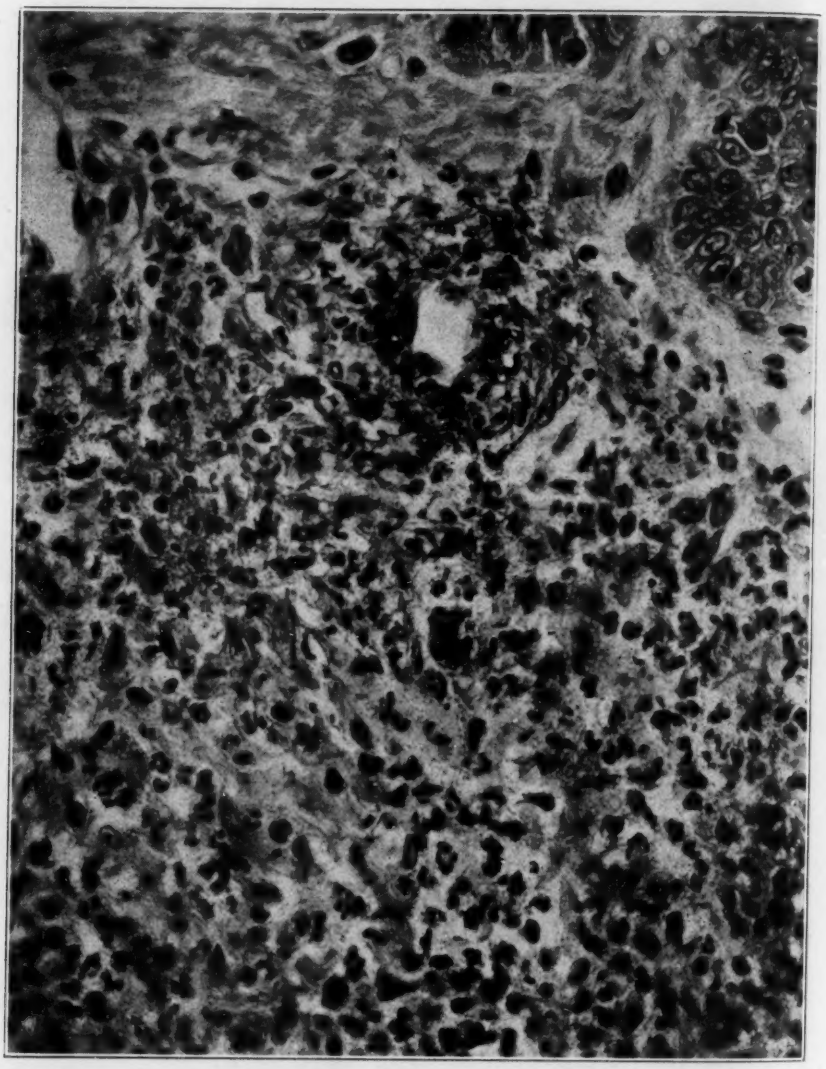

Fig. 3.—Section taken in 1942. Phloxine–methylene blue stain. A capillary surrounded by a dense infiltrate is shown. At the right lower quadrant of the capillary, swollen reticulum fibers are visible. (Normal reticulum fibers are not visible in phloxine–methylene blue stains); × 375.

cultures resulted in no growth from the lower portion. Nonhemolytic streptococci grew in aerobic cultures from the upper portion. This growth was regarded as a contaminant, since saliva contains abundant nonhemolytic streptococci.

Histologic Studies.—Four specimens for biopsy were obtained from the larger lesion on the left cheek, 1 in 1942 and 3 in 1945.

The section obtained in 1942 showed an epidermis of normal thickness. The rete cones were nearly all flattened out. An extensive, extremely cellular infiltrate occupied the corium (fig. 2). It was separated from the epidermis by a narrow rim of normal connective tissue. In the upper half of the corium the infiltrate was continuous; in the lower half it had essentially a perivascular arrangement. Here and there the infiltrate extended between the fat cells of the subcutaneous fat. The infiltrate was composed of many cell types: eosinophils, polymorphonuclear leukocytes, histiocytes (reticulum cells or monocytes), phagocytes, foam cells, fibroblasts, lymphocytes, plasma cells and mast cells. Although their proportionate number varied from place to place, eosinophils predominated everywhere. Most of them were polymorphonuclear, but some had a round nucleus. Neutrophils were fairly numerous, and in many instances it was impos-

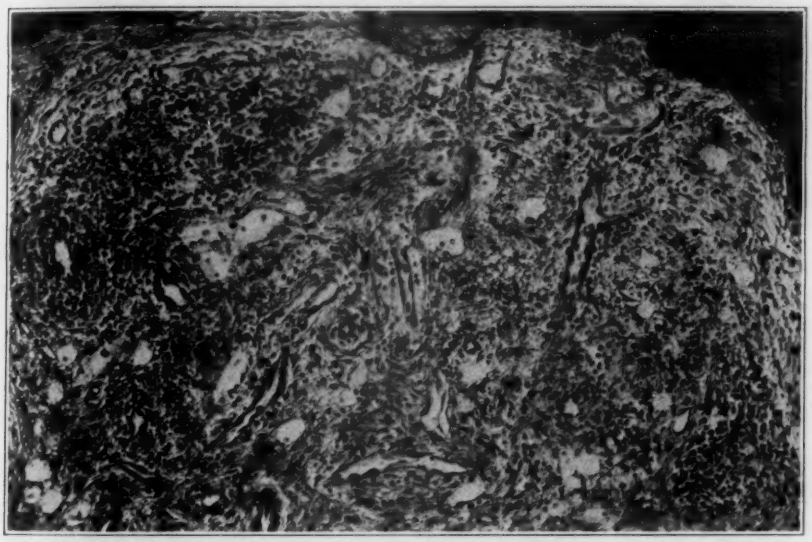

Fig. 4.—Section taken in 1945. Aniline–methylene blue stain. The cellular infiltrate is patchy and separated by areas of fibrosis. Histiocytes and lymphocytes predominate. Numerous swollen reticulum fibers are visible. Foam cells are scattered throughout the field; × 120.

sible to decide whether a cell was a neutrophil or an eosinophil. There were numerous histiocytes with large, pale, round or oval nuclei. Some of the histiocytes exhibited phagocytic properties, containing hemosiderin granules, fat vacuoles or both. A few large foam cells were present. In some areas the histiocytes showed development into fibroblasts. Lymphocytes and plasma cells were scattered in small numbers through the infiltrate. Mast cells were conspicuous because of their size and number. The blood vessels of the corium were dilatated and their endothelium swollen. The cellular infiltrate was particularly dense in their vicinity. Phloxine-methylene blue stain (which does not stain normal reticulum fibers) showed swollen, intensely eosinophilic reticulum fibers around many of the blood vessels (fig. 3). Thus the impression was gained that the vessels were

arterioles with greatly thickened and infiltrated walls. Elastic tissue stains, however, revealed no elastic fibers around the vessels and proved that the vessels were capillaries and precapillaries with perivascular infiltration.

The sections obtained in 1945 revealed slight hyperkeratosis with dilatation and keratotic plugging of some of the pilosebaceous follicles. The infiltrate was no longer continuous, but divided into irregular islands by areas of fibrosis (fig. 4).

Fig. 5.—Section taken in 1945. Reticulum stain (Foot). There is a dense network of reticulum fibers. Many of them are swollen. On the right side and in the lower part of the field various stages of transformation of reticulum fibers into collagen fibers can be seen. Foam cells are present in the upper corium; × 200.

In a few places the infiltrate was still composed predominantly of eosinophils and neutrophils, but in general it consisted mainly of histiocytes and lymphocytes. Many histiocytes contained vacuoles and hemosiderin granules. Foam cells were

conspicuous. At the periphery of the islands of infiltrate there were many fibroblasts laying down young connective tissue. Many swollen reticulum fibers were visible in phloxine-methylene blue and aniline blue (Mallory) stains. Reticulum stains stained after Foot (fig. 5) showed a dense reticulum network within the cellular infiltrate; in many areas one could observe the gradual transformation of

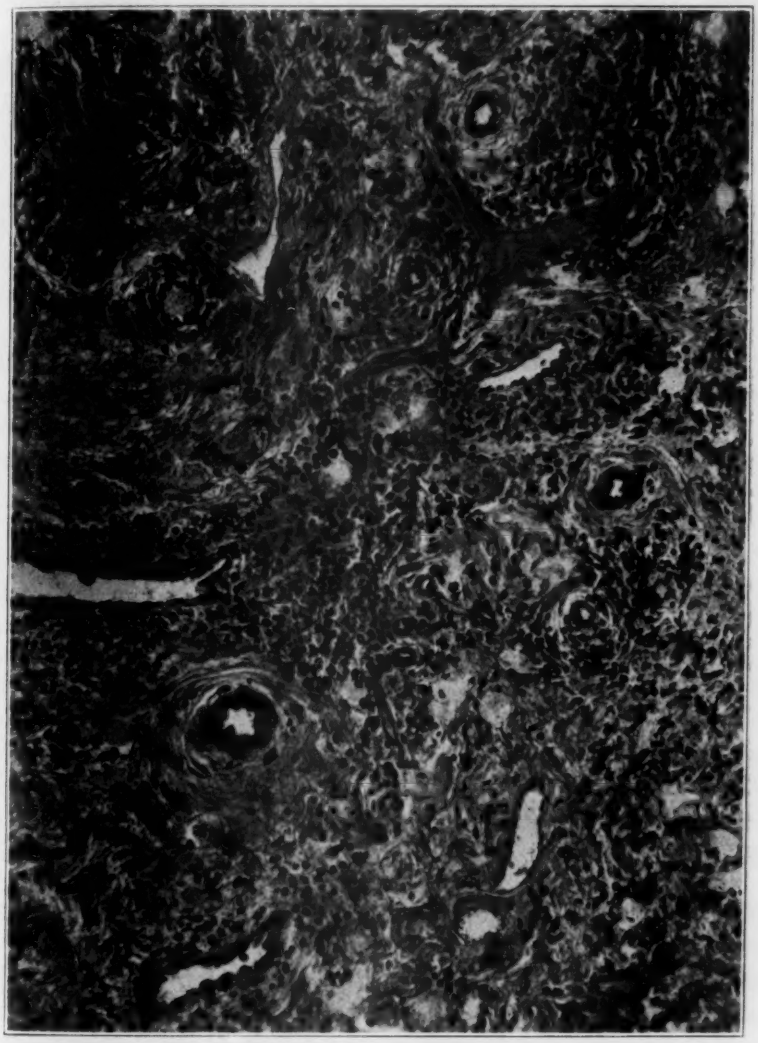

Fig. 6.—Section taken in 1945. Phloxine-methylene blue stain. There is a considerable degree of fibrosis. Several vessels show thickening and fibrosis of their walls. The perivascular infiltrate of such vessels has been replaced by concentrically arranged collagen bundles; × 250.

reticulum fibers into connective tissue fibers. The endothelial cells lining the blood vessels were large and increased in number. Some of the vessels located in areas of fibrosis had thick, fibrotic walls (fig. 6). Polariscopic examination of stained

frozen sections revealed that the fat vacuoles within the phagocytes and the content of the foam cells were doubly refractile. This indicated that the fat contained cholesterol and cholesterol esters.

COMMENT

The clinical picture suggests the following diseases: sarcoid, xanthoma tuberosum, erythema elevatum diutinum and eosinophilic granuloma. On histologic grounds the first two can both be excluded, but erythema elevatum diutinum and eosinophilic granuloma deserve consideration.

Before discussing these two diseases, I wish to call attention to 2 cases recently reported by Anderson [1] and Netherton [2] which show a striking resemblance to the case reported in this paper and probably represent the same disease.

In Anderson's case, a woman aged 42 presented four lesions, one on each side of the neck and one on each cheek. They were sharply marginated, slightly raised, plaquelike and erythematous with a distinct yellowish tinge. They had developed slowly in the course of nine years. The serum cholesterol content was normal. The following clinical diagnoses were considered: lupus erythematosus, xanthoma and sarcoid. A biopsy showed "xanthoma with definite fatty infiltration." No details of the histologic appearance were given.

In Netherton's case, a woman aged 45 presented—on both cheeks, on the bridge of the nose and on the right ear—fairly well demarcated, raised, rounded and irregularly shaped plaques. The lesions had developed over a period of ten years. The more recent lesions were light red, the older lesions yellowish. The overlying epidermis was smooth; the pilosebaceous follicles were dilatated. Histologic examination revealed an infiltrate composed of lymphocytes, fibroblasts, epithelioid cells and both large and small foam cells. The capillaries were dilatated, and their endothelial cells were hyperplastic. In some areas the stroma was dense and fibrous, with less cellular infiltrate. A fat stain showed intracellular and extracellular deposits of doubly refractile lipids. Netherton thought that lupus erythematosus with superimposed xanthomatous infiltrate was the most likely diagnosis but pointed out that the histologic changes were not entirely consistent with lupus erythematosus. Weidman, in his discussion of Netherton's paper, raised the question whether this case, as well as all cases of extracellular cholesterosis, may not be erythema elevatum diutinum with superimposed extracellular cholesterosis.

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1. Anderson, N. P.: (*a*) A Case for Diagnosis (Xanthoma?), Arch. Dermat. & Syph. **48**:471 (Oct.) 1943; (*b*) Systemic Xanthoma, ibid. **49**:149 (Feb.) 1944.

2. Netherton, E. W.: Chronic Discoid Lupus Erythematosus With Superimposed Xanthomatous Infiltration, Arch. Dermat. & Syph. **51**:100 (Feb.) 1945.

The histologic picture of Netherton's case greatly resembles that presented by the later sections of the case reported herein. The only difference lies in the presence of eosinophils and neutrophils in my case. Since their number was much smaller in the later than in the earlier sections, it is conceivable that future sections, if taken, may not show any of these cells, so that the resemblance to Netherton's case would then be complete.

1. Erythema Elevatum Diutinum.—This is a rare dermatosis. In a review of the literature only 20 cases were found to which this diagnosis could be applied without reservation. Of these, 14 belonged to the "Hutchinson type" [3] and 6 to the "Bury type." [4] The early lesions of erythema elevatum diutinum are papules and nodules which may, by peripheral extension and by confluence with neighboring lesions, increase into large plaques. Their color is red or purplish, their consistency soft to moderately firm. The most commonly involved sites are the extensor surfaces of the extremities, particularly the areas overlying the joints. Next commonly, the face, ears and buttocks are affected. In most cases the number of lesions is considerable; in 2 cases, however,

3. (*a*) Hutchinson, J.: On Two Remarkable Cases of Symmetrical Purple Congestion of the Skin in Patches, with Induration, Brit. J. Dermat. **1**:10, 1888-1889; (*b*) Two Additional Cases of Purple Patches on the Skin: History of Gout in Both, Arch. Surg. **1**:372, 1889-1890. (*c*) Audry, C.: Des érythémato-scléroses et, particulièrement, de l'érythémato-sclérose pemphigöide, Ann. de dermat. et syph. **5**:1, 1904. (*d*) Dalla Favera, G. B.: Beiträge zum Studium des sogenannten Granuloma annulare (R. Crocker); éruption circinée chronique de la main (Dubreuilh), Dermat. Ztschr. **16**:73, 1909; (*e*) Erythema elevatum diutinum und Granuloma annulare, ibid. **18**:541, 1910. (*f*) Piccardi, G.: Erythema elevatum et diutinum, Dermat. Wchnschr. **55**:1115, 1912. (*g*) Frühwald, R.: Fall von Erythema elevatum, ibid. **63**:995, 1916. (*h*) Weidman, F. D.: Xanthoma en tumeurs, Arch. Dermat. & Syph. **11**:566 (April) 1925; (*i*) Erythema Elevatum Diutinum, ibid. **14**:622 (Nov.) 1926. (*j*) Weidman, F. D., and Besançon, J. H.: Erythema Elevatum Diutinum: Rôle of Streptococci, and Relationship to Other Rheumatic Dermatoses, ibid. **20**:593 (Nov.) 1929. (*k*) Combes, F. C., and Bluefarb, S. M.: Erythema Elevatum Diutinum, ibid. **42**:441 (Sept.) 1940. (*l*) Engman, M. F., Jr.; Pfaff, R. O., and Cooper, Z. K.: Erythema Elevatum Diutinum, ibid. **45**:334 (Feb.) 1942. (*m*) Ketron, L. W.: Erythema Elevatum Diutinum, ibid. **50**:363 (Dec.) 1944.

4. (*a*) Bury, J. S.: A Case of Erythema with Remarkable Nodular Thickening and Induration of Skin, Associated with Intermittent Albuminuria, Illust. M. News **3**:145, 1889. (*b*) Hutchinson, J.: Peculiar Disease of Skin of Hands (Bury's Case), Arch. Surg. **2**:301, 1890-1891 [plate 61], (*c*) Crocker, H. R., and Williams, C.: Erythema Elevatum Diutinum, Brit. J. Dermat. **6**:1 and 33, 1894. (*d*) Smith, F. J.: A Case of So-Called Erythema Elevatum Diutinum, ibid. **11**:144, 1894. (*e*) Zweig, L.: Ueber einen Fall von Erythema elevatum et diutinum, Arch. f. Dermat. u. Syph. **109**:519, 1911. (*f*) Trimble, W. B.: Erythema Elevatum Diutinum: Report of a Case, with Comments on Its Nosologic Positions, Arch. Dermat. & Syph. **13**:383 (March) 1926. (*g*) Gray, A. M. H.: Erythema Elevatum Diutinum, Proc. Roy. Soc. Med. **25**:1743, 1932.

(Trimble's case [4f] and Hutchinson's fourth case [3b]) there were only two plaques, and in 2 others, (Gray's case 4[g] and Hutchinson's third case [3b]) a single plaque. In Hutchinson's fourth case the two plaques were located on the forehead. The evolution of the lesions may follow several courses: they may persist as soft plaques (Hutchinson type); they may develop into hard, fibrotic, keloid-like plaques (Bury type), or they may undergo involution. The color of the soft plaques may remain purple or change to a yellowish brown. The yellowish tint is, according to Weidman,[5] caused by hemoglobin or hematin. The duration of erythema elevatum diutinum may be from one to many years. In Piccardi's case [3f] the disease lasted fourteen months, in Dalla Favera's second case [3e] two and a half years. In all other cases the disease was still active at the time of reporting. In 5 cases [6] the disease had already persisted for five years or longer.

Histologic examination was carried out in 15 cases, that is, in all except those reported by Hutchinson [3a,b] and Bury.[4a,b] For practical purposes the histologic picture may be divided into three stages. In the first stage (Hutchinson type) the microscopic picture is dominated by a dense infiltrate in which polymorphonuclear leukocytes predominate. They show no tendency to disintegrate. In addition to the polymorphonuclear leukocytes, lymphocytes, plasma cells, histiocytes, fibroblasts and, occasionally, epithelioid cells [3k,l] and mast cells [7] are present. In 3 cases [8] a few eosinophils, and in 1 case [3k] numerous eosinophils were observed. The capillaries usually are dilatated and their endothelium swollen. The perivascular reticulum fibers may show hyaline degeneration.[9] In the second stage, the cellular infiltrate has decreased in density and has essentially a perivascular arrangement. Polymorphonuclear leukocytes and lymphocytes are fewer, and fibroblasts predominate. There is beginning fibrosis separating the cellular infiltrate into irregularly shaped islands. In the third stage (Bury type) fibrosis dominates the picture. The cellular infiltrate is greatly reduced, and polymorphonuclear leukocytes are entirely absent. Frequently, the walls of the capillaries also show fibrosis. Evidence of phagocytosis was present in 4 cases: Dalla Favera [3d,e] described in his 2 cases the presence of phagocytes containing erythrocytes and nuclear debris; Engman [3l] observed hemosiderin within phagocytes; Trimble [4f] noticed foci of large cells with foamy cytoplasm.

5. Weidman, F. D.: The Pathology of the Yellowing Dermatoses, Arch. Dermat. & Syph. **24**:954 (Dec.) 1931.

6. Hutchinson.[3a] Weidman.[3h,i] Weidman and Besançon.[3j] Engman.[3l] Ketron.[3m] Trimble.[4f]

7. Audry.[3c] Dalla Favera.[3d,e] Piccardi.[3f]

8. Dalla Favera.[3d] Weidman.[3h,i] Weidman and Besançon.[3j] Ketron.[3m]

9. Dalla Favera.[3e] Weidman.[3h,i] Weidman and Besançon.[3j] Combes.[3k] Engman.[3l] Ketron.[3m]

2. Eosinophilic Granuloma. — Eosinophilic granuloma has been described in two organs, the bone and the skin. In no case were osseous and cutaneous lesions present simultaneously. Whether eosinophilic granuloma of the bone and of the skin represent the same disease has so far not been discussed in the literature.

(*a*). Eosinophilic Granuloma of the Bone: This is a benign, destructive lesion affecting one, several or many bones. The first instance was recorded in the literature by Finzi [10] in 1929, but only in 1940 did Otani and Ehrlich [11] and Lichenstein and Jaffe [12] establish eosinophilic granuloma of the bone as a well defined disease entity. Up to the present a total of 44 cases have been described.[13] Locally there may be swelling, tenderness and pain, but some lesions are asymptomatic. With the possible exception of the bones of the hands and feet, any bone may be the site of lesions. Mainly the cranial vault, the ribs, the vertebrae, the humeri and the femurs are involved. The

10. Finzi, O.: Mieloma con prevalenza della cellule eosinofile, circoscritto all'osso frontale in un giovane di 15 anni, Minerva med. **9**:239, 1929.

11. Otani, S., and Ehrlich, J. C.: Solitary Granuloma of Bone Simulating Primary Neoplasm, Am. J. Path. **16**:479, 1940.

12. Lichtenstein, L., and Jaffe, H. L.: Eosinophilic Granuloma of Bone, with Report of a Case, Am. J. Path. **16**:595, 1940.

13. (*a*) Mignon, F.: Ein Granulationstumor des Stirnbeins, Fortschr. a. d. Geb. d. Röntgenstrahlen **42**:749, 1930. (*b*) Schairer, E.: Ueber eine eigenartige Erkrankung des kindlichen Schädels (Osteomyelitis mit eosinophiler Reaktion), Zentralbl. f. allg. Path. u. path. Anat. **71**:113, 1938. (*c*) Eosinophilic Granuloma of Bone, Cabot Case 26302, New England J. Med. **223**:149, 1940. (*d*) Hatcher, C. H.: Eosinophilic Granuloma of Bone, Arch. Path. **30**:828 (Sept.) 1940. (*e*) Farber, S.: The Nature of "Solitary or Eosinophilic Granuloma" of Bone, Am. J. Path. **17**:625, 1941. (*f*) Green, W. T., and Farber, S.: "Eosinophilic or Solitary Granuloma" of Bone, J. Bone & Joint Surg. **24**:499, 1942. (*g*) Bass, M. H.: Solitary Eosinophilic Granuloma of Bone, Am. J. Dis. Child. **61**:1254 (June) 1941. (*h*) Gross, P., and Jacox, H. W.: Eosinophilic Granuloma and Certain Other Reticuloendothelial Hyperplasias of Bone, Am. J. M. Sc. **203**:673, 1942. (*i*) Thoma, K.: Eosinophilic Granuloma with Report of One Case Involving First the Mandible, Later Other Bones, and Being Accompanied by Diabetes Insipidus, Am. J. Orthodontics (Oral Surg. Sect.) **29**:641, 1943. (*j*) Jaffe, H. L., and Lichtenstein, L.: Eosinophilic Granuloma of Bone: A Condition Affecting One, Several or Many Bones, but Apparently Limited to the Skeleton, and Representing the Mildest Clinical Expression of the Peculiar Inflammatory Histiocytosis Also Underlying Letterer-Siwe Disease and Schüller-Christian Disease, Arch. Path. **37**:99 (Feb.) 1944. (*k*) Mallory, T. B.: Medical Progress: Pathology, Diseases of the Bone, New England J. Med. **227**:955, 1942. (*l*) Schairer, E.: Osteomyelitis mit eosinophiler Reaktion (Eosinophiles Granulom des Knochens), Deutsche Ztschr. f. Chir. **258**:637, 1944. (*m*) Engelbreth-Holm, J.; Teilum, G., and Christensen, E.: Eosinophil Granuloma of Bone—Schüller-Christian's Disease, Acta med. Scandinav. **118**:292, 1944. (*n*) Solomon, H. A., and Schwartz, S.: Eosinophilic Granuloma of Bone, J. A. M. A. **128**:729 (July 7) 1945. Finzi.[10] Otani and Ehrlich.[11] Lichtenstein and Jaffe.[12]

lesions were single in 31 and multiple in 13 of the 44 cases described. The lesions tend to heal spontaneously in the course of several months or years and are radiosensitive.

Histologic examination in the early stage reveals a granulomatous process in which two types of cells, eosinophils and histiocytes (reticulum cells), predominate. The eosinophils usually are polymorphonuclear, but occasionally [14] mononuclear eosinophils are also present. Finzi,[10] Farber [13e,f] and Thoma [13i] regarded them as eosinophilic myelocytes. Jaffe and Lichtenstein,[13j] however, stated that they were too small to be regarded as such. The histiocytes are actively phagocytic and may contain cellular debris,[15] finely divided lipid [16] or hemosiderin.[17] The lipid as a rule is isotropic, but occasionally it is anisotropic.[18] There are, in addition, variable numbers of plasma cells, lymphocytes and polymorphonuclear leukocytes. Not infrequently phagocytic multinuclear giant cells are found.[19] There may be foci of necrosis and hemorrhage.[20] Numerous capillaries are present. The endothelial cells of the capillary walls may be swollen.[13h] Jaffe and Lichtenstein observed multiplication of the adventitial cells and their transformation into histiocytes.

At a later stage the number of eosinophils is greatly reduced; they may even be entirely absent.[13e,f] Histiocytes are then the most commonly found type. They frequently are vacuolated and may assume the appearance of foam cells.[21] The fat which they contain usually is isotropic, but may be anisotropic.[22] In addition, there is ingrowth of fibroblasts. Fibroblasts increase in number as the lesion ages, and

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14. Finzi.[10] Farber.[13e] Green and Farber.[13f] Thoma.[13i] Jaffe and Lichtenstein.[13j]

15. Finzi.[10] Lichtenstein.[12] Hatcher.[13d] Farber.[13e] Green and Farber.[13f] Jaffe and Lichtenstein.[13j]

16. Otani and Ehrlich.[11] Schairer.[13b] Farber.[13e] Green and Farber.[13f] Bass.[13g] Gross and Jacox.[13h] Thoma.[13i] Jaffe and Lichtenstein.[13j] Engelbreth-Holm, Teilum and Christensen.[13m]

17. Otani and Ehrlich.[11] Lichtenstein and Jaffe.[12] Schairer.[13b,l] Farber.[13e] Green and Farber.[13f] Jaffe and Lichtenstein.[13j]

18. Farber.[13e] Green and Farber.[13f] Jaffe and Lichtenstein.[13j] Engelbreth-Holm, Teilum and Christensen.[13m]

19. Finzi.[10] Otani and Ehrlich.[11] Schairer.[13b,l] Footnote 13*c*. Farber.[13e] Green and Farber.[13f] Bass.[13g] Gross and Jacox.[13h] Thoma.[13i] Engelbreth-Holm, Teilum and Christensen.[13m]

20. Otani and Ehrlich.[11] Hatcher.[13d] Farber.[13e] Green and Farber.[13f] Bass.[13g] Jaffe and Lichtenstein.[13j] Schairer.[13l] Solomon and Schwartz.[13n]

21. Otani and Ehrlich.[11] Farber.[13e] Green and Farber.[13f] Jaffe and Lichtenstein.[13j] Gross and Jacox.[13h] Engelbreth-Holm, Teilum and Christensen.[13m]

22. Farber.[13e] Green and Farber.[13f] Engelbreth-Holm, Teilum and Christensen.[13m]

gradually the granulomatous process is replaced by connective tissue.[23] Jaffe and Lichtenstein presented evidence that eosinophilic granuloma may heal through resolution instead of through the intermediary steps of lipidization and connective-tissue scarring.

Farber [13e,f] first recognized the pathogenesis of eosinophilic granuloma correctly. He concluded that eosinophilic granuloma, Hand-Schüller-Christian disease and Letterer-Siwe disease represented "variations in degree, stage of development and localization of the same basic disease process." With one exception,[13l] all authors [24] who have since written on eosinophilic granuloma of the bone have accepted this point of view. These three diseases are now regarded as histiocytoses (reticuloendothelioses). The concept of Hand-Schüller-Christian disease as a primary disturbance of the lipid metabolism (xanthomatosis) has been abandoned [13k] and the presence of cholesterol is regarded as a secondary infiltration. If the histiocytosis occurs in infancy it is generalized and rapidly fatal (Letterer-Siwe disease), and the time required for development of the lesion into a lipogranuloma is not available. In early childhood the disease is chronic (Hand-Schüller-Christian disease) and lipidization usually is pronounced, with few or no eosinophils. In later childhood or in adulthood the usual picture is that of eosinophilic granuloma. Transitional cases between these three forms of histiocytosis are on record.[25]

Letterer-Siwe disease and Hand-Schüller-Christian disease affect the skin, in addition to the bones and other organs, in about a third of the cases.[26] On the other hand, cutaneous lesions have never been described in conjunction with eosinophilic granuloma of the bone.

(*b*). Eosinophilic Granuloma of the Skin: The first cases (later classified as eosinophilic granuloma of the skin by the author himself) were described by Martinotti [27] in 1923. Nanta and Gadrat [28] established the term eosinophilic granuloma of the skin in 1937. Eleven cases in

23. Otani and Ehrlich.[11] Farber.[13e] Green and Farber.[13f] Gross and Jacox.[13h]

24. Bass.[13g] Gross and Jacox.[13h] Thoma.[13i] Jaffe and Lichtenstein.[13j] Mallory.[13k] Engelbreth-Holm, Teilum and Christensen.[13m] Solomon and Schwartz.[13n]

25. Farber.[13e] Green and Farber.[13f] Gross and Jacox.[13h] Engelbreth-Holm, Teilum and Christensen.[13m]

26. Lane, C. W., and Smith, M. G.: Cutaneous Manifestations of Chronic (Idiopathic) Lipoidosis (Hand-Schüller-Christian Disease), Arch. Dermat. & Syph. **39**:617 (April) 1939.

27. Martinotti, L.: (*a*) Contributo allo studio della eosinofilia istiogena cutanea, Arch. per le sc. med. **46**:259, 1923; (*b*) Zur Frage des eosinophilen Granuloms, Dermat. Wchnschr. **112**:25, 1941.

28. Nanta, A., and Gadrat, J.: Sur un granulome éosinophilique cutané, Bull. Soc. franç. de dermat. et syph. **44**:1470, 1937.

all have been recorded with this diagnosis.[29] Whereas the cases described as eosinophilic granuloma of the bone represent a well established entity both clinically and histologically, those described as eosinophilic granuloma of the skin show uniformity only in their histologic, but not in their clinical, appearance. Probably not all cases described as eosinophilic granuloma should be regarded as such. On the basis of the clinical data supplied, it appears advisable to exclude Martinotti's 3 cases [27] and Lapière's case.[29e] Martinotti's case 1 probably represented a pyogenic ulcer, his case 2 a systemic moniliasis and his case 3 an allergic eruption. Lapière's case was one of malignant lymphoma (Hodgkin's disease). Of the remaining 7 cases, 5 [30] were clinically characterized by nodular and plaquelike lesions of chronic course. In 2 cases [31] the lesions were vegetating. The latter 2 cases appeared sufficiently different from the other 5 cases to make one suspect that they represented a different disease.

Because of the complexity of the clinical picture in most of the reported cases, it is impossible to delineate each case adequately in a limited space. The reader is referred to the reviews recently published by Martinotti [27b] and Cerutti.[29e] However, since the literature on eosinophilic granuloma of the skin has never been reviewed in the English language literature, a short abstract of each reported case will be given.

Martinotti's first patient [27] was a young soldier who for several months had had on one leg an ulcer the size of a large coin and surrounded by an area of infiltration of doughy consistency. Excision of the ulcer was followed by recovery.

Martinotti's second patient [27] had a diffuse cutaneous eruption composed of papules, nodules, vesicles and pustules. The patient recovered after many months. Cryptococcus ruber Demme was obtained from the cutaneous lesions, the blood and the urine on several occasions.

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29. (*a*) Freund, E.: Su un caso di strani tumori cutanei in una tuberculosa, Dermosifiligrafo **5**:617, 1930. (*b*) Pautrier, L. M.; Glasser, R., and Labourgade, A.: Lésions vérruqueuses, végétantes, éléphantiasiformes, du pourtour de l'orifice anal, de tout le pli fessier et du scrotum, s'accompagnant de lésions végétantes endorectales pouvant faire penser à une maladie de Nicolas-Favre, mais de nature indéterminée, Bull. Soc. franç. de dermat. et syph. **43**:896, 1936. (*c*) Lapière, S.: Un cas de granulome éosinophilique, Bull. Soc. franç. de dermat. et syph. **44**:1479, 1937. (*d*) Pasini, A.: Granuloma eosinofilo (reticulo-endoteliosi proliferativa), Gior. ital. di dermat. e sif. **81**:1, 1940. (*e*) Cerutti, P.: Il granuloma eosinofilo, Dermatologica **85**:90, 1942. (*f*) Lewis, G. M.: A Case for Diagnosis (Erythema Nodosum?), Arch. Dermat. & Syph. **48**:436 (Oct.) 1943; (*g*) Eosinophilic Granuloma, ibid. **51**:144 (Feb.) 1945. (*h*) Wigley, J. E. M.: ?Sarcoid of Boeck; ?Eosinophilic Granuloma, Brit. J. Dermat. **57**:68, 1945. Martinotti.[27a,b] Nanta and Gadrat.[28]

30. Freund.[29a] Pasini.[29d] Cerutti.[29e] Lewis.[29f,g] Wigley.[29h]

31. Nanta and Gadrat.[28] Pautrier, Glasser and Labourgade.[29b]

In Martinotti's third patient [27] the illness lasted only fifteen days. Large umbilicated bullae on infiltrated red bases were present on the dorsa of both hands.

Freund's patient [29a] showed livid red, hard, painless nodes of six years' duration on face, shoulders and extremities. Roentgen ray therapy resulted in the patient's recovery.

Pautrier, Glasser and Labourgade [29b] reported the case of a patient with extensive perianal and endorectal vegetating lesions of six months' duration.

Nanta and Gadrat's patient [28] had perianal and endorectal vegetating lesions similar to those of the preceding patient and, in addition, vegetating tumefactions of the gums. The lesions were still progressing when the patient was last seen, nearly two years after the onset of the disease.

In Lapière's patient [29c] the disease began with an erythematous, bullous, papular and nodular eruption of generalized distribution. These lesions continued to appear for years but were then gradually superseded by hypertrophic sclerotic lesions. Sixteen years after the onset of the disease numerous large, hard lymph nodes were first felt. Soon afterward, the patient died of his disease.

Cerutti[29e] observed a patient in whom numerous nodular lesions of generalized distribution had been present for three months. In the more severely involved areas the nodules had coalesced into large plaques. In the genitocrural folds the lesions resembled syphilitic condylomas. Roentgen ray therapy caused the rapid disappearance of all the lesions. Soon afterward, however, the patient died, of lymphosarcoma of the cervical lymph nodes.

In Lewis' patient,[29f,g] crops of erythematous nodes and plaques had been appearing and disappearing for more than three years. They cleared without scarring. The majority of the lesions were located on the lower extremities.

The following 2 cases closely resemble the case reported in this paper:

Pasini's patient [29d] first noticed an indurated plaque on the right side of her forehead eight years before her admission to the hospital for treatment. This slowly increased in size until, finally, it covered all of the right half of the forehead and part of the left half. Three years before admission two other plaques had appeared, symmetrically placed before and below each ear. Two years before admission a fourth plaque had appeared in the submental region. The lesions presented a rounded, elevated border and a convex tumefaction covered by normal epidermis. They had a nearly homogeneous red cyanotic color and were of hard elastic consistency. Roentgen ray therapy resulted in the almost complete clearing of the lesions.

Wigley's patient [29h] presented on her forehead and nose four lesions which had appeared during the two years preceding her admission. They were smooth, grayish brown, slightly raised and infiltrated. They varied in size up to 1 cm.

Histologic examination revealed a similar picture in all but Lapière's case.[29c] This case presented, in addition to the large number of eosinophils, numerous atypical reticulum cells and, in Lapière's own opinion, was one of "malignant reticulo-endotheliosis." The histologic appearances of the remaining 10 cases may be discussed together. They showed a dense polymorphous infiltrate of the corium. In some cases [32] this infiltrate extended into the subcutaneous fat. In others it had led to erosion of the epidermis and to ulceration. Eosinophils and histiocytes predominated. Martinotti,[27] Pasini [29d] and Cerutti [29e] observed not only polymorphonuclear but also mononuclear eosinophils and histiocytes with eosinophilic granules. They observed intermediary stages between these forms of eosinophils and regarded the eosinophils as of histiogenic rather than of myeloic origin. In addition, polymorphonuclear leukocytes, lymphocytes, plasma cells and fibroblasts were present in varying amounts. In 5 cases [32] mast cells, and in 3 cases [33] epithelioid cells were present. Giant cells, resembling either megakaryocytes or Langhans' cells, were observed in 1 case.[29a] The infiltrate was well vascularized and, frequently, the endothelial cells and the walls of the vessels showed proliferation.[34] The evolution of eosinophilic granuloma is as yet little known. Only one author, Pautrier,[29b] reported the histologic appearance of an early and of a late lesion. In the late lesion the eosinophils had almost entirely disappeared; the infiltrate was more monomorphous, consisting mainly of plasma cells and lymphocytes, and was divided into islands by the ingrowth of collagen. Beginning fibrosis was noted also by Freund [29a] and Pasini.[29d]

3. *Relation of Eosinophilic Granuloma of the Skin to Eosinophilic Granuloma of the Bone and to Erythema Elevatum Diutinum.*—(*a*) Eosinophilic Granuloma of the Skin and of the Bone: Only one writer, Freudenthal,[35] has so far drawn attention to the fact that in the medical literature two diseases have been described under the name of eosinophilic granuloma, one as occurring in the skin and the other as occurring in the bones. He has assumed that they are identical, but has given no reasons for his belief.

In favor of their being the same disease is the great similarity of their histologic appearance. However, this is in no way specific, since many types of granulation tissue contain eosinophils and histiocytes.

32. Martinotti.[27a,b] Freund.[29a] Pasini.[29d]
33. Martinotti.[27a,b] Freund.[29a] Cerutti.[29e]
34. Martinotti.[27a,b] Freund.[29a] Pasini.[29d] Cerutti.[29e]
35. Freudenthal, W., in discussion on Wigley.[29h]

It is only by their greater prevalence in this disease that eosinophilic granuloma stands out. In addition both diseases usually show polymorphonuclear leukocytes and plasma cells. Evolution appears similar in that either resolution or collagenization takes place. In the process of collagenization the eosinophilic element diminishes and may even disappear entirely.

The differences between the two diseases are as follows: In eosinophilic granuloma of the bone, phagocytosis of cell fragments, lipids and hemosiderin by histiocytes is a prominent feature, and foam cells may occur, whereas in the cases described as eosinophilic granuloma of the skin phagocytosis and foam cells have never been noted. Furthermore, the lesions in eosinophilic granuloma of the bone tend to heal spontaneously, usually within a year, whereas in eosinophilic granuloma of the skin they may persist indefinitely.

As to pathogenesis, both types of eosinophilic granuloma may be classified as inflammatory histiocytoses; but while eosinophilic granuloma of the bone can be connected with Letterer-Siwe disease and Hand-Schüller-Christian disease (mainly through the tendency of its histiocytes to phagocyte fat and to transform themselves into foam cells), no such connection is, so far, apparent for eosinophilic granuloma of the skin. It may therefore be concluded that, although it is likely that the two diseases are related, final proof is still lacking.

(*b*). Eosinophilic Granuloma of the Skin and Erythema Elevatum Diutinum: A comparison of the clinical features of eosinophilic granuloma of the skin and erythema elevatum diutinum is difficult because of the variable clinical picture presented by the cases reported with the diagnosis of eosinophilic granuloma of the skin. However, in the 5 patients [30] whose cutaneous eruption consisted of nodular and plaque-like lesions of red or purplish color, the clinical appearance was similar to that described in erythema elevatum diutinum.

Histologic examination reveals in both diseases a cellular granulation tissue in which polymorphonuclear cells predominate. In erythema elevatum diutinum the majority are neutrophils, in eosinophilic granuloma eosinophils. This is the only major difference; otherwise the histologic picture in the two diseases shows great similarity. In both diseases histiocytes are present, though in varying numbers. They are, as a rule, more prominent in eosinophilic granuloma. The phagocytic activity of the histiocytes (which is so pronounced in eosinophilic granuloma of the bone) is no important feature in either erythema elevatum diutinum or eosinophilic granuloma of the skin. It has never been observed in eosinophilic granuloma of the skin, and is rare in erythema elevatum diutinum, having been described in only 4

36. Deleted by the author.

cases.[37] In addition to leukocytes and histiocytes, there are found lymphocytes, fibroblasts and, occasionally, plasma cells and mast cells in the histologic picture of both diseases. The vascular walls may be invaded by the cellular infiltrate and show evidence of degeneration, both in erythema elevatum diutinum [9] and in eosinophilic granuloma.[38] In both diseases the infiltrate may persist essentially unchanged, may resolve or may gradually be replaced by fibrous tissue.

Thus, it appears that there is sufficient similarity in the clinical and the histologic appearance of both eosinophilic granuloma of the skin and erythema elevatum diutinum to permit speculation as to a possible relationship.

NOSOLOGIC POSITION OF THE REPORTED CASE

In its clinical appearance the case reported could pass as an instance of the early stage of erythema elevatum diutinum. Although numerous lesions are the rule in erythema elevatum diutinum, in 4 cases from the literature there were only one or two lesions. The presence of soft, purplish partly yellowish plaques, the absence of subjective symptoms and the chronicity of the lesion are consistent with a diagnosis of erythema elevatum diutinum. Histologically, the presence of neutrophils and the degeneration of the perivascular reticulum fibers in the first biopsy and the beginning fibrosis in the later biopsies are compatible with a diagnosis of erythema elevatum diutinum. Yet, the two most striking features of the case were the presence of a great number of eosinophils and foam cells. These are uncommon features for erythema elevatum diutinum, since eosinophils were observed in only 4 cases and foam cells in only 1 case.

Compared with eosinophilic granuloma of the skin, the case reported bears, in its clinical appearance, great resemblance to the cases described by Pasini [29d] and Wigley,[29h] in which there were plaquelike lesions limited to the face. In contrast to Pasini's case roentgen ray therapy did not cause improvement of the lesions. In its histologic appearance, the case resembles eosinophilic granuloma of the skin, so far as it showed a dense polymorphous infiltrate in which eosinophils predominated. The vascular changes seen have been noted also in some cases of eosinophilic granuloma of the skin. The only major difference consists in the pronounced phagocytic activity of the histiocytes and the presence of foam cells in the case reported.

In contrast to eosinophilic granuloma of the skin, phagocytic activity is conspicuous in eosinophilic granuloma of the bone, resulting in the accumulation of hemosiderin and fat in the histiocytes and the formation of foam cells. It can thus be stated that the histologic picture,

37. Dalla Favera,[3d,e] Engmann, Pfaff and Cooper,[3b] Trimble.[4f]
38. Martinotti,[27a,b] Freund.[29a]

with its predominance of eosinophils and foam cells, resembles that of eosinophilic granuloma of the bone more than that of either eosinophilic granuloma of the skin or erythema elevatum diutinum. If one would accept the diagnosis of eosinophilic granuloma in the case presented, it would provide an argument in favor of the identity of eosinophilic granuloma of the skin and of the bone.

In conclusion, the diagnosis in the case reported must remain open. It is suggested that the case is one of eosinophilic granuloma of the skin, a disease which may be related both to eosinophilic granuloma of the bone and to erythema elevatum diutinum.

SUMMARY

A woman has had for ten years three gradually enlarging soft plaques on her cheeks. Histologic examination in 1942 revealed an extremely cellular, granulomatous infiltrate in which eosinophils and histiocytes predominated. A few foam cells were also present. Histologic sections obtained three years later revealed a considerable decrease in the number of eosinophils but an increase in the number of foam cells and a beginning fibrosis.

No description of any dermatosis with this histologic picture was encountered in the literature. The histologic appearance was identical with that of eosinophilic granuloma of the bone. In many aspects it resembled that of eosinophilic granuloma of the skin and of erythema elevatum diutinum.

A diagnosis of eosinophilic granuloma of the skin is suggested.

It is possible that eosinophilic granuloma of the skin, eosinophilic granuloma of the bone and erythema elevatum diutinum are related diseases. These three diseases have in common, in the early stage, a granulomatous, extremely cellular infiltrate in which neutrophils or eosinophils predominate. This infiltrate may persist, may resolve or undergo fibrosis. In the fibrotic stage neutrophils and eosinophils are few and may be entirely absent. Phagocytic cells containing lipid and hemosiderin, and foam cells may or may not be present.

GRANULOMATOUS HODGKIN'S DISEASE OF THE SKIN WITH EXTREME EOSINOPHILIA

(Eosinophilic Granuloma of the Skin?)

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COMMONLY, Hodgkin's disease expresses itself on the skin in a nonspecific manner, such as by pruritus, urticaria and scaly erythrodermas. Relatively seldom do granulomatous lesions appear. In our case, five biopsies of specimens of the skin and two of specimens of the lymph nodes furnished an unusual opportunity for correlation of the reactions in these two tissues and for observation of the tissue processes from their beginning to maturity. Moreover, polymorphonuclear leukocytes were present in enormous numbers; the neutrophilic ones, which are so rare in this disease, bespoke an acute type of reaction, and the eosinophilic ones raised the question of whether eosinophilic granuloma of the skin was related.

REPORT OF A CASE

The patient was first seen at Grady Hospital on May 29, 1935, with a complaint of painful menstruation. The past history was essentially noncontributory and insignificant. The blood pressure was 160 systolic and 95 diastolic. The other physical findings were essentially normal. The patient was not seen again until June 26, 1941, when she returned with a complaint of pains in her arms and shoulders and also of "food souring" in her stomach. She complained of gastric distress after eating potatoes and beans. The physical examination revealed no significant findings, and she improved under symptomatic treatment.

On May 26, 1943, the patient returned to the medical clinic, with the following history: About a year previously, soreness appeared in the left side of the neck, "like taking a cold in the neck." It lasted only a few days, but it reappeared nine months later, in February 1943. She used a liniment, and the pain again disappeared only to recur in two months. With the onset of this pain a "knot" also appeared in the left side of her neck, two days after dental work had been done. During the next four weeks it neither increased nor receded.

The family history was essentially noncontributory. The patient's mother and father were living and well. Three brothers died early in infancy; one brother died of injuries. One brother was living and well. There was no past history of any serious illness in the immediate family.

The patient was born in Georgia Dec. 10, 1908. She had been married for fifteen years. Her husband was living and well. There was one pregnancy, and her only son, aged 13 years, was living and well. She worked as a maid and used tobacco and alcohol in moderation. Occasional constipation was treated with

infusion of senna with magnesium sulfate. Acetylsalicylic acid was taken infrequently for headaches or any pain.

The past history was noncontributory except for measles and mumps in childhood and the symptoms mentioned previously. The blood pressure was as follows: 200 systolic and 130 diastolic in the left arm and 190 systolic and 124 diastolic in the right arm. The temperature was 98 F. and the pulse rate 80, and the respirations numbered 20 per minute.

The patient appeared to be a well nourished, slender woman 35 years old and was seemingly in good health. The skin was of fine texture, and no abnormalities were seen. The hair, bones, joints and muscles appeared normal. There was a small, palpable, lymph node in the right cervical region and also an enlarged one in the left supraclavicular area, about 2 cm. in diameter, just above and behind the midportion of the left clavicle. It was indurated, nontender and freely movable. The eyes were normal except for a grade I sclerosis of the arterioles on ophthalmoscopic examination. The nose, ears and throat were normal. Three teeth were missing; no pyorrhea or other infection was present. The thorax and lungs revealed no abnormalities. The cardiac findings were reported as follows: "The apex pulse is located 10 cm. from the midline in the fifth interspace. The heart is enlarged to the left and extends 11 cm. from the midline in the fifth interspace. There is no thrill, the sounds are of full quality and the rhythm is regular. There is a grade I blowing systolic murmur heard best just to the left of the sternum in the third interspace. The aortic sound is tambor-like."

The abdominal and pelvic findings were normal. The results of neurologic examination were normal. The laboratory findings on May 26, 1943 were as follows: As to the blood, the red blood cells numbered 4,290,000 and the white blood cells 5,200. The hemoglobin content measured 11.4 Gm. (73 per cent). The differential count revealed basophils 1, eosinophils 1, polymorphonuclears 62, lymphocytes 34 and monocytes 2. The urinalysis gave normal results. On June 4, 1943, the red blood cells numbered 4,200,000 and the white blood cells 8,200. The hemoglobin content measured 9.8 Gm. (63 per cent). The differential count revealed 56 polymorphonuclears, 32 lymphocytes, 7 eosinophils and 5 monocytes. The Kahn reaction of the blood was negative. A roentgenogram of the chest showed a heart somewhat enlarged to the left and aortic in type. Both pulmonary fields were clear. There was no evidence of mediastinal or hilar adenopathy.

On July 13 the differential cell count of the blood was substantially the same, barring a reduction to 4 eosinophils. Again, the examination of the urine resulted negatively.

On July 15, 1943 the glands in the left cervical area were dissected. An attempt was made to remove the entire mass of matted nodes, but it was impossible owing to the extensiveness of the process. During the manipulation, one of the nodes was broken and caseous material escaped. A portion of the mass was removed for biopsy, the report of which was tuberculous adenitis. In August 1943, the patient was again examined and no change was found. The glandular enlargement was the same.

The patient disappeared from observation until May 16, 1944. She stated that following the operation the original nodule remained the same for about three months. Afterward, it began to grow. It reached a considerable size, burst and has been draining since. In January 1944 a private surgeon removed a large part of the mass, following which a draining sinus has persisted. In addition, there were numerous large indurated areas in the left side of the neck. The left breast was extremely tender; its lower two thirds were homogeneously swollen, and the areola was thick. The surrounding skin was atrophic and shiny. At about

10 o'clock and 3 cm. from the nipple, there was an extremely hard and tender spot. Over the upper portion of the breast there was an infiltrated cutaneous nodule, and a few were present over the anterior wall of the chest. The left arm was slightly swollen, especially around the elbow. In the left axilla numerous fairly soft, slightly elevated nodules were present. An enormous, soft node was present in the left side of the neck, just below the ear. Several enlarged nodes were present in the submaxillary and sublingual regions. Many hard discrete nodes were present at the base on the right side of the neck.

The laboratory findings resulted as follows: The red blood cells numbered 3,450,000 and the white blood cells 23,500; the hemoglobin measured 52 per cent. In the differential count, the polymorphonuclears were 80 per cent, lymphocytes 9 per cent, monocytes 3 per cent, basophils 1 per cent and eosinophils 7 per cent. Polychromatophilia and a certain degree of anisocytosis and poikilocytosis were present. The urinalysis gave normal results.

A biopsy was performed on one of the nodules on the chest on May 17, 1944. The report was as follows: "Sections reveal a peculiar granulomatous condition of the dermis. It bears considerable resemblance to Hodgkin's disease but does not seem to be that disease. The lesions are both circumscribed and diffuse. The cells are chiefly fibroblasts and epithelioid cells. Among these there are many lymphocytes, macrophages and giant cells. Some of the latter resemble foreign body giant cells, whereas others are more like tumor cells. They contain from 4 to 10 nuclei. Again, numerous eosinophils may be seen. Sternberg-Reed cells are not noted. This does not look like a lymphoma of any type. It is some peculiar sort of granuloma. No specific organisms can be found."

On August 16 filtered roentgen ray therapy was administered over the left supraclavicular area, over the left axilla and over the lesions on the chest. The exposures given were 100 r units about every four days. Filtration of 3.5 mm. of aluminum was used at 190 kilovolts and 8 milliamperes. In spite of this treatment, the condition became progressively worse, and on Aug. 28, 1944 the patient presented decided edema and elevation of temperature of the right breast. Numerous nodules on the left side of the chest became greatly enlarged and ulcerated. Roentgen ray treatment of the right breast was begun, and the swelling began to subside. The larger nodular lesions on the left side of the chest became more numerous and ulcerated. A photograph was taken at this time. The roentgen ray therapy was continued, and from this date the lesions began to improve gradually but some of the small, deep nodules continued to increase in size and ulcerate. The treatment was continued until September 25. On this date the areas involved received a total dosage which varied from 5,000 to 6,000 r units of filtered radiation (3.5 mm. of aluminum). On Oct. 16, 1944 the patient returned for a check-up and seemed much improved. A blood cell count resulted as follows: The white blood cells numbered 9,800. In the differential count, the polymorphonuclears were 39 per cent, lymphocytes 7 per cent, monocytes 6 per cent, basophils 2 per cent and eosinophils 51 per cent.

The condition remained stationary, and on Dec. 20, 1944, the patient was referred to the dermatology clinic. The dermatologic findings were as follows: Both breasts were hard and infiltrated and pitted on pressure. The impression was that of considerable fibrosis with edema. Radiation changes were present on the skin of both breasts. On the upper half of the left breast there were numerous deep subcutaneous nodules, 2 mm. to 2 cm. in diameter. They seemed to be attached to the deep tissues. The skin was movable over the nodules. The older nodules were larger and elevated above the level of the skin. The overlying skin was inflamed but intact except for desquamation over a few. The largest nodules,

which apparently were of the longest duration, appeared in two forms. First, a few 3 to 4 cm. in diameter were inflamed and hard; the skin was not movable over them and appeared atrophic. Second, numerous lesions 1 to 4 cm. in diameter were hard and infiltrated, and the center was ulcerated. The ulcer was punched out, crateriform and covered by a thin serous exudate or crust. When the crust was removed the base was red and raw. The nodules extended laterally to the left

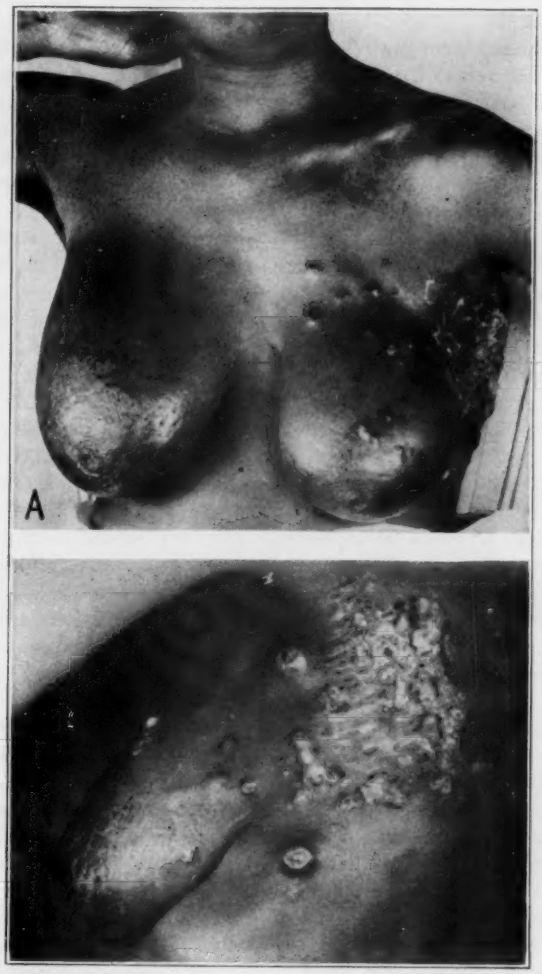

Fig. 1.—*A*, the lesions at their height, at the front of the chest. *B*, lesions on the back.

wall of the chest and posteriorly to the left scapula. On the back, several large ulcerated nodules were present. Between the large nodules numerous small ones, 1 to 2 mm. in diameter, were present, capped by a soft seborrheic-like scale, which was easily removed. When the scale was removed, a shiny dry papule was exposed. The papules were so numerous and so closely set that in some areas

they fused into plaques. When the scales were rubbed off, the individual papules, as described, stood out clearly. The cutaneous lesions were nontender and not painful.

The patient was hospitalized. She had a constant fever, with an irregular temperature curve, mostly between 100 and 103 F.

A pitting edema appeared in both upper extremities, extending from midarm to the wrist and also on the mons pubis and left thigh. A generalized lymphadenopathy was present, the nodes being discrete, firm and freely movable. Those on the left side of the neck were definitely tender. The nodes showing the greatest enlargement were the submental, right axillary, right inguinal and right epitrochlear. The veins of the neck were distended. The observations on examination of the chest were normal. A firm, nodular mass 5 to 6 cm. in diameter was present in the left fornix. Other findings were essentially normal.

The laboratory findings at this time were as follows: The Kahn reaction of the blood was negative, and routine tests of the urine resulted normally. The red blood cells numbered 4,200,000 and the white blood cells 50,900. The hemoglobin content measured 12.2 Gm. The polymorphonuclears were 23 per cent, lymphocytes 3 per cent, and eosinophils 74 per cent. On Dec. 28, 1944 the white blood cells numbered 50,000. In the differential count, the polymorphonuclears were 15 per cent, lymphocytes 1 per cent and eosinophils 84 per cent. On Jan. 9, 1945 the white blood cells numbered 60,600, with a differential count of polymorphonuclears 18 per cent, lymphocytes 5 per cent, monocytes 2 per cent and eosinophils 75 per cent. The examination of the stool gave normal results. The nonprotein nitrogen content measured 25 mg. and the cholesterol content of the blood 130 mg. Roentgen examination of the chest showed no appreciable changes. There was no enlargement of the hilar shadows. There were no changes in the bones.

A biopsy was performed on an inguinal node and the report on the microscopic examination was as follows: "No normal lymphoid tissue is seen. Most of the tissue is fibrous, with a great many lymphocytes of various types present. Most of these are large cells. Numerous multinucleated cells of the Sternberg-Reed type are present. There are innumerable eosinophils present elsewhere. Histologically, this is an instance of Hodgkin's disease."

A biopsy specimen of another cutaneous nodule was sent to Dr. Fred D. Weidman, who reported as follows: "The surface of the lesion is superficially ulcerated. In the corium, a rounded nodule of peculiar granulation tissue appears, which extends to the deepest parts of the skin. Various kinds of cells are disposed on a delicate fibrous reticulum which has replaced entirely the normal collagenous structure. Most conspicuous are the enormous numbers of eosinophilic polymorphonuclears, but an equal number of neutrophils is intermixed. However, suppuration is not indicated at any place. From place to place, a few large monocytes are discoverable, and sometimes they are concentrated into a given area but still remain isolated. They are multinucleate and conform to Sternberg-Reed cells, barring the extreme rarefaction of their cytoplasms and their indefinite outlines. The nucleus is usually degenerated, and, accordingly, these cells should be regarded as being in a state of hydropic degeneration. The fibrosis of the reticulum which is usual in Hodgkin's disease is scantily developed. Blood vessels ramify richly through the infiltration; they are frequently dilated and engorged by eosinophilic polymorphonuclears." Dr. Weidman was unwilling to make a final diagnosis of Hodgkin's disease at this time.

Summary of History of Case.—Over a period of at least three (and, doubtless, more) years, deep and ulcerated granulomas developed in the lymph nodes and

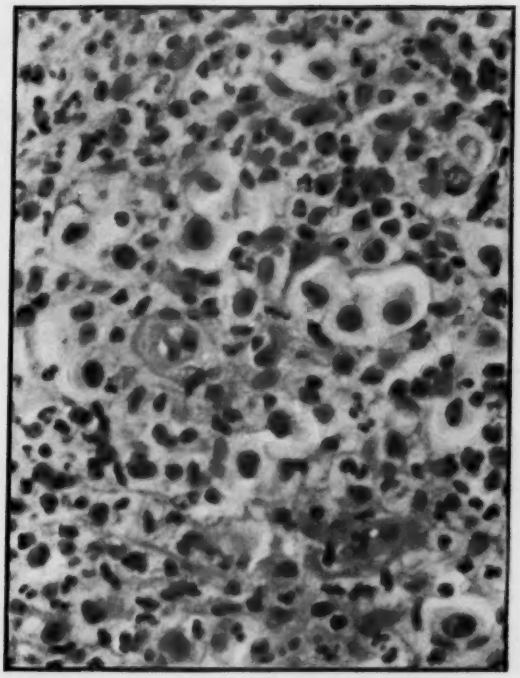

Fig. 2.—Early granuloma of the skin, illustrating the large clear cells that are regarded as monocytes. The eosinophilia was not so extreme in this region as at others. Polymorphonuclear neutrophils are numerous. Sternberg-Reed cells did not appear in early lesions such as this one was.

skin of a 35 year old Negro woman. They began in the left side of the neck, and although they were concentrated on the upper left side of the thoracic wall they finally extended to the right breast. Eventually, a generalized lymphadenopathy appeared and attacks of fever. Anemia gradually developed (as low as 3,450,000 red blood cells and with a hemoglobin content of 52 per cent), together with an eosinophilia (absent at first), which finally reached 84 per cent. There was not any evidence of enlargement of the liver and spleen. Extremely heavy doses of roentgen rays resulted in definite but only temporary benefit. The histologic processes in the skin were not diagnostic for any entity; at first there was not any tissue eosinophilia, but eventually it became extreme indeed. The diagnosis of Hodgkin's disease was delayed because the histologic picture remained atypical for a long time, and was clinched only when a biopsy of a lymph node was performed.

HISTOPATHOLOGY

Altogether, five specimens of skin and two of lymph nodes were studied. The largest lesion from the skin measured 2 cm. in diameter and the smallest 0.5 cm. It was thus possible to study the disease in both young and old lesions and to learn that there was considerable variation in the two. Inasmuch as eosinophilic granuloma is a new arrival in dermatology, it is proper to record the pathologic processes in detail, whether it proves to be a separate entity or not. Moreover, with five specimens of skin at hand, an unusual opportunity was afforded to learn something of the range of histologic changes that are possible in Hodgkin's disease (as in young and old lesions).

Skin.—When ulceration was present, regeneration was highly developed at the margins, amounting almost to pseudoepitheliomatous hyperplasia. Even in early lesions, the epidermis was definitely acanthotic (and edematous). This was to be expected when such large masses of polymorphonuclears were present in the corium, because products of degeneration which must be developed in such extreme leukocytic processes can diffuse into the epidermis and produce a hyperplasia of its cells. This would be the case whether the leukocytic hyperplasia is fundamental to the Hodgkin's disease in this case or not.

It was in the corium, though, that the significant processes occurred. In early lesions, diffuse masses of special granulation tissue replaced all the normal structures. The stroma was delicately reticular and did not include any definite fibrous tissue strands, such as are so useful in the diagnosis of Hodgkin's disease. The infiltrative cells were nearly equally divided between lymphocytes and polymorphonuclears, together with small numbers of monocytes and numerous atypical Sternberg-Reed cells. Goodly numbers of capillaries ramified regularly through the infiltration; their walls were thick because their endothelial cells were hyperplastic and swollen. In one specimen they were highly dilated and engorged by eosinophilic polymorphonuclears. The tissue eosinophils comprised an estimated 50 to 75 per cent of all the polymorphonuclears

and at some places had accumulated into masses comprised almost solely of such cells. The Sternberg-Reed cells were numerous and tended to accumulate in certain localities. They were not typical; although they were sometimes multinucleate, their cytoplasms were highly rarefied and reticular, and their outlines were indefinite. Indeed, it was not certain that they were in fact such cells until the biopsy of the inguinal node disclosed the typical ones.

In older lesions, the cellular infiltrative mass became broken up into irregularly shaped areas, the patterning of which suggested that they were arranged in interlacing, broad, most irregularly shaped tracts or bundles that were reminiscent of the patterning of sarcoma (the so-called Hodgkin's sarcoma?). Now, lymphocytes comprised a moderate majority of all the cells. A smaller percentage of the polymorphonuclears was eosinophilic, estimated at 30 to 40 per cent, and indeed in one specimen they were limited to a few widely scattered but still sizable aggregations. A few strands of young fibrocellular tissue could now be discovered at widely separated positions, thus adding an important item in the diagnosis of Hodgkin's disease. Blood vessels became definitely reduced in numbers. Sternberg-Reed cells were also relatively few and had changed from the rarefied form to one with a solid cytoplasm and a definite outline. Histiocytes now dominated the picture, with the result that the eosinophils and lymphocytes appeared to be scattered at intervals by contrast with the density with which they occurred in the early lesions. They were outstandingly spindle in shape and, occurring as they did in bundles, contributed to the resemblance to sarcoma that was previously mentioned.

The Lymph Nodes.—In a specimen from a "caseated" node, the architecture of lymph node could not be identified; evidently the lesion had become so large that only a part of it was submitted for microscopic examination. It consisted mostly of adult fibrous tissue, within which various foci of cellular infiltration were located. In them, lymphocytes and polymorphonuclears were present in approximately equal numbers; the latter tended to occur in small, illy defined foci. Eosinophils were few and widely scattered. Monocytes were relatively few. The Sternberg-Reed cells were abundant and typical. The large numbers of polymorphonuclears being barred, the picture was typical for Hodgkin's disease.

A second specimen likewise came from a large node, but it is not known whether it had undergone caseation. In any event, a young cellular fibrosis was developed throughout the section and the Sternberg-Reed cells were numerous and typical. With these two exceptions, the picture was of the order of that exhibited in early cutaneous lesions. That is, the lymphocytes and polymorphonuclears were numerous indeed and were present in approximately equal numbers; many of the latter

were eosinophilic, and monocytes were relatively few. Moreover, a few of the latter had the large, clear cytoplasms and indefinite outlines that were described previously in early lesions of the skin.

The rarefaction of the Sternberg-Reed cells prompted a test for fat, but tissue from the lymph nodes alone was available for frozen sections. Sudan III preparations did not disclose fat in them, but there were great numbers of minute globules free in the tissue spaces and small numbers in the monocytes. Typical foam cells were not developed though; the general form of the monocyte was preserved, and it was swollen only slightly.

Analysis of the Histologic Changes.—Hodgkin's disease will be dealt with first. The full complement of diagnostic criteria appeared only in the lymph nodes and in the older examples of cutaneous lesions. For the skin, particularly at fault was the development of fibrosis and of unequivocal Sternberg-Reed cells; indeed, early lesions exhibited no fibrosis, and Sternberg-Reed cells were few and atypical. The number of monocytes varied widely; in fact, they were numerous in only one of the older cutaneous lesions (the one described as sarcomatoid in its patterning).

The ensemble speaks for varying degrees in acuteness (speaking in terms of tissue processes) of the Hodgkin processes. For the skin, acuteness is indicated by the absence of fibrosis and by the rarefied (hydropic) type of Sternberg-Reed cell, and it must be added that the latter cells were also represented in the actively proliferative part of one of the lymph nodes. Second, the picture speaks for tardiness in the development of the more chronic (mature and more diagnostic) features in the skin. This is in keeping with clinical knowledge that the cutaneous expressions are dominantly nonspecific (urticaria and similar conditions); it is seldom that typical granulomatous lesions of Hodgkin's disease are observed in the skin, and the dermatopathologist, too, seldom observes the same, and typical, picture that he is so familiar with in the lymph nodes. In the light of this case, even though the cutaneous lesions were of many months' duration, the processes in the skin remained young and immature in type; they did not nearly approach those of the lymph nodes. This intimates, once again, that certain forces are operative in the skin (immunologic?) which are not operative at least in the lymph nodes and perhaps in other tissues. Incidentally, Tuft[1] approached this topic when he demonstrated that typhoid agglutinins were more highly developed after injections into the skin than after intravenous ones.

This case, then, assists in the arrival at the following generalizations in respect to Hodgkin's disease. It is tardy in affecting the skin if it

1. Tuft, L.: The Skin as an Immunological Organ, with Results of Experimental Investigations and Review of Literature, J. Immunol. **21**:85 (Aug.) 1931.

does so at all. When it does involve the skin, the lesions are usually nonspecific, histologically as well as clinically. In the rare cases in which granulomatous lesions develop, the tissue reaction is relatively acute in type; seldom indeed does the final, fibrous reaction occur such as is so familiar in the lymph nodes. One of us (F. D. W.) has studied a case in which the patient at necropsy had great numbers of cutaneous nodules. For years, these lesions had been regarded as various diseases, including psoriasis and seborrheic dermatitis. She had been presented, too, at a meeting of the Chicago Dermatological Society, but Hodgkin's disease was not suspected. The typical histologic picture was not exhibited in any of the several nodules examined. The cellular infiltrate consisted almost entirely of lymphocytes. Moderate numbers of monocytes represented the most that could be construed in favor of Hodgkin's disease. Incidentally, their cytoplasms, too, were highly hydropic and their outlines indefinite.

The histopathology will be discussed next from the standpoint of the eosinophila and eosinophilic granuloma. Tissue eosinophilia was just as extreme in the "acute" lymph nodes as in the skin but was not as spectacular, because the fibrous matrix diluted, so to speak, all the infiltrative cells. They thus became scattered over a wider area; they were not condensed, as in the skin. Still, the proportion of eosinophils to neutrophils and to monocytes was just as high as in the skin. That is, the eosinophilic response per se was as great in the lymph node. Incidentally, whether the eosinophilic leukocytes bespeak an acute type of reaction or not, the neutrophils must. The nuclei were almost invariably bilobate or multilobate and could not be interpreted as eosinophilic myelocytes.

What is the significance of the eosinophilia in our case? The simplest explanation is that the Hodgkin's disease was complicated by some general eosinophilogenic condition such as trichinosis, hookworm disease or allergy. In such case, the superabundant eosinophils of those diseases would be represented by eosinophilia in the tissue reaction of the Hodgkin lesions. The second theory would concern hemopoietic tissue, in the direction of the myelocytes and monocytes particularly. The literature on eosinophilic granuloma of the skin is replete with discussion centering around eosinophilic myelocytes, and that on eosinophilic granuloma of bone naturally revolves around the hemopoietic tissue in bone marrow. In short, there may be a common ground for the two eosinophilic granulomas (bone and skin) and Hodgkin's disease through the medium of hemopoietic tissue.

At this juncture, the introduction of fat into the picture in our case brings Letterer-Siwe disease into the case. By now, it appears to be the consensus that Hand-Christian disease, Letterer-Siwe disease and eosinophilic granuloma of bone are members of the same fundamental

disease processes. The latter are best known as they are seen in Hand-Christian disease and have to do with a monocytic hyperplasia which is attended by lipidal infiltrations. The details cannot be discussed here; suffice it to point out that in our patient both the monocytic and the fatty changes were represented. If it should develop in the future that eosinophilic granuloma of the skin qualifies as an entity when the eosinophilia is combined with some leukosis (including monocytic disease like Hodgkin's disease), our case would automatically qualify as one of eosinophilic granuloma, and all cases of Hodgkin's disease would fall into that category when they were accompanied with eosinophilia. This thinking is too extreme in the present state of our knowledge, and, accordingly, our case should be regarded for the present simply as one of Hodgkin's disease, but with an extraordinary degree of eosinophilia.

CONCLUSIONS

In Hodgkin's disease, granulomatous lesions are relatively rare in the skin. They develop tardily and incompletely compared with those in the lymphadenoid tissues.

It would appear that in the initial stages the tissue reaction in the skin is far more acute in type than that in the lymph nodes, perhaps more acute than ever occurs in the lymph nodes, and in our case the extreme polymorphonuclear neutrophil reaction was particularly significant. The fibrosis and the development of Sternberg-Reed cells are so seldom exhibited in the skin that the dermatopathologist is denied this assistance in diagnosis in a way that is not the case for the general pathologist. Lymph nodes are far more promising leads toward histologic diagnosis than the skin.

The extraordinary eosinophilia in our case may or may not be significant for an interrelationship with eosinophilic granuloma. It remains to be demonstrated whether the scope of Letterer-Siwe disease is sufficiently broad genetically to include Hodgkin's disease, but the demonstration of fat in a lymph node of our patient may be significant.

TREATMENT OF VARIOUS TYPES OF CUTANEOUS TUBERCULOSIS WITH PROMIZOLE AND STREPTOMYCIN

A Preliminary Report

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THIS preliminary report on treatment of certain types of cutaneous tuberculosis and tuberculids is part of a study of various agents in the treatment of tuberculosis that was started several years ago by two of us (Feldman and Hinshaw).[1] This report deals with the clinical application to cutaneous tuberculosis of promizole [2] and streptomycin,[3] which were found to be the least toxic and have demonstrated the greatest therapeutic effect of any of the substances which were used in treatment of tuberculous guinea pigs.

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1. (*a*) Feldman, W. H.; Hinshaw, H. C., and Mann, F. C.: Effects on Experimental Tuberculosis of 4,2′-Diaminophenyl-5′-Thiazolesulfone (Promizole): Preliminary Report, Proc. Staff Meet., Mayo Clin. **19**:25-33 (Jan. 26) 1944. (*b*) Feldman, W. H., and Hinshaw, H. C.: Effects of Streptomycin on Experimental Tuberculosis in Guinea Pigs: Preliminary Report, ibid. **19**:593-599 (Dec. 27) 1944 (*c*) Hinshaw, H. C.; Feldman, W. H., and Pfuetze, K. H.: Clinical Administration of 4,2′-Diaminophenyl-5′-Thiazolesulfone (Promizole) in Tuberculosis: Preliminary Report, ibid. **19**:33-36 (Jan. 26) 1944. (*d*) Feldman, W. H.; Hinshaw, H. C., and Mann, F. C.: Streptomycin in Experimental Tuberculosis, Am. Rev. Tuberc. **52**:269-298 (Oct.) 1945. (*e*) Hinshaw, H. C., and Feldman, W. H.: Streptomycin in Treatment of Clinical Tuberculosis: A Preliminary Report, Proc. Staff Meet., Mayo Clin. **20**:313-318 (Sept. 5) 1945.

2. Supplied by Dr. L. L. Bambas and Dr. E. A. Sharp, Parke, Davis & Company, Detroit.

3. Supplied by Dr. D. F. Robertson and Dr. J. M. Carlisle, of Merck & Co., Inc., Rahway, N. J., and by Dr. George Hazel, of the Abbott Laboratories, North Chicago, Ill.

Since Ehrlich developed the satisfactory arsenical for treatment of syphilis, a constant search has been made for some similarly effective agent for the treatment of tuberculosis. Although results with use of metallic substances have been unsuccessful, with the advent of the sulfonamide compounds, the sulfones and, shortly afterward, the antibiotic agents, investigation in this field was stimulated again.

Rich and Follis,[4] in 1938, were the first to report on the influence of sulfanilamide in treatment of tuberculosis in guinea pigs. They reported that retardation in the development of tuberculosis in guinea pigs was observed, although the drug did not in any instance arrest the disease. The drugs of the sulfone series, promin (sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate), diasone (disodium formaldehyde sulfoxylate diaminodiphenyl sulfone) and promizole (4,2′-diaminophenyl-5′-thiazolylsulfone), were found actually to arrest tuberculosis in infected guinea pigs; however, enthusiasm has decreased because on clinical use in many cases minimal therapeutic effect was noted and varying degrees of toxic reactions were encountered.

With the introduction of penicillin, hope was again revived that the course of tuberculosis could be altered by a specific substance; however, penicillin was found to have no effect against the disease. Nonetheless, continued efforts revealed that other substances that could be extracted from living micro-organisms were able to suppress growth of bacteria which produce disease. The most outstanding of these substances are streptothricin and streptomycin, which were discovered by the group of investigators who worked with Waksman.[5] Both are derived from soil-inhabiting fungi (Actinomyces lavendulae and Actinomyces griseus) and have the ability to inhibit the growth of Mycobacterium tuberculosis in test tubes. Streptomycin is well tolerated by guinea pigs, and in about a third of the animals it will eradicate advanced tuberculosis. In the majority of the remaining two thirds, the disease may be regarded as arrested after its use.[1b] Streptothricin is toxic to guinea pigs, and its influence on tuberculosis is less favorable than that of streptomycin.

We have treated 15 patients who had various forms of cutaneous tuberculosis, consisting of lupus vulgaris, scrofuloderma, tuberculosis cutis colliquativa, erythema induratum, primary inoculation tuberculosis, tuberculosis miliaris disseminata faciei and papulonecrotic tuberculids. Eight of the 15 patients received promizole, and 7 received

4. Rich, A. R., and Follis, R. H., Jr.: The Inhibitory Effect of Sulfanilamide on the Development of Experimental Tuberculosis in the Guinea Pig, Bull. Johns Hopkins Hosp. **62**:77-84 (Jan.) 1938.

5. Waksman, S. A.; Bugie, E., and Schatz, A.: Isolation of Antibiotic Substances from Soil Micro-Organisms, with Special Reference to Streptothricin and Streptomycin, Proc. Staff Meet., Mayo Clin. **19**:537-548 (Nov. 15) 1944.

streptomycin; 3 of the patients who had received promizole first were treated subsequently with streptomycin. Of the 15 cases, only 12 will be reported in this paper.

PROMIZOLE

Promizole was synthesized first by Bambas.[6] The average dose for adults is 8 to 16 Gm. per day, and it is administered orally. In our cases the larger doses in this range occasionally produced toxic reactions, which were minimized considerably when the dose was reduced to 8 or 10 Gm. daily. When this dose was administered each day for periods ranging from approximately six weeks to four months, from 500 to about 1,200 Gm. of the drug was given. The following reports of 4 cases illustrate the effect of promizole on scrofuloderma, lupus vulgaris and erythema induratum.

CASE 1.—*Scrofuloderma.*—A white woman 49 years of age began to have suppurative cervical adenitis on the left side in April 1941. After that, similar lesions had developed in the cervical and axillary regions on the right side. Many of the glandular abscesses had been incised, and others had ruptured spontaneously. All had persistent draining sinuses. The patient had lost 20 pounds (9.1 Kg.) in two years.

Roentgenologic examinations of the chest gave negative results. Material from a sinus in the cervical region was used for the inoculation of guinea pigs, which subsequently gave positive reactions for Myco. tuberculosis. The tuberculin test performed with first strength purified protein derivative elicited a positive reaction. The sedimentation rate was 118 mm. per hour (Westergren method).

Treatment with promizole was begun on Dec. 22, 1943. The patient received approximately 500 Gm. in the following four weeks, and some clinical improvement was believed to have occurred during this time. The drug, however, produced some nausea and anorexia. The level of hemoglobin dropped 1 Gm. during administration.

The patient has since reported that no significant improvement has occurred.

CASE 2.—*Lupus vulgaris.*—A white woman 62 years of age had had an erythematous infiltrated plaque involving the left ala, septum and bulb of the nose three years previous to her admission to the clinic in August 1944. Several small apple jelly nodules were found on diascopy. A biopsy specimen revealed the typical architecture of lupus vulgaris, but no tubercle bacilli were seen in the section.

The patient's general health was good. Roentgenologic examination of the chest gave negative results, and the routine laboratory findings were within normal ranges.

A total of 1,250 Gm. of promizole was administered in four months, being started on Aug. 8, 1944. The drug was well tolerated except for slight anorexia late in the period of treatment.

No significant improvement was observed in this period of treatment.

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6. Bambas, L. L., cited by Feldman, W. H.; Hinshaw, H. C., and Mann, F. C.: Promizole in Tuberculosis: The Effect on Previously Established Tuberculosis of Guinea Pigs of 4,2′-Diaminophenyl-5′-Thiazolylsulfone (Promizole), Am. Rev. Tuberc. **50**:418-440 (Nov.) 1944.

CASE 3.—*Erythema induratum.*—A white woman aged 37 years had had recurring crops of discrete ulcerative lesions low on the anterior and medial aspects of the legs for twenty years prior to her admission to the clinic in January 1944. The lesions had been painful, discrete nodules, which ulcerated and eventually healed, leaving an atrophic pigmented scar. The lesions had occurred chiefly in the summer months.

At the time of admission, several ulcers were present and a zone of infiltration measured 1 inch (2.5 cm.) in diameter (fig. 1 *a*). A biopsy specimen revealed erythema induratum. Cultures of the specimen removed and results of examinations of inoculated guinea pigs were negative for Myco. tuberculosis. The sedimentation rate was 30 mm. per hour (Westergren). The patient's general health was good. The Mantoux test elicited a positive reaction, but a roentgenogram of the chest was negative for tuberculosis.

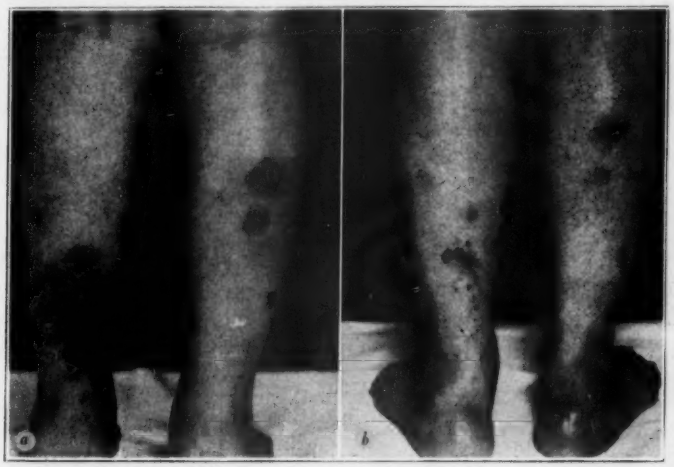

Fig. 1 (case 3).—Erythema induratum. *a*, Jan. 1, 1944; *b*, healed lesions after treatment with 750 Gm. of promizole. The patient remained well for more than a year, when the lesions recurred.

Treatment with promizole was started on Jan. 12, 1944 and was continued for six consecutive weeks. A total of about 500 Gm. was given. The ulcerations were judged to be about half healed at the end of this time.

She returned in June 1944. In one month during this interval she had taken approximately 250 Gm. of promizole. At the time of the patient's return the ulcers were all healed, and they remained so during the entire summer (fig. 1 *b*) and the following winter. This was remarkable for this patient, as she always had had the lesions during the summer months.

In September 1945, the patient reported that several small ulcers had recurred on each leg.

CASE 4.—*Scrofuloderma.*—The patient, a white man 33 years of age, stated that suppurative adenitis had begun in the cervical and axillary regions in 1942. The affected lymph nodes ultimately had ruptured, ulcerated and produced persistently draining sinuses. The patient had lost about 30 pounds (13.6 Kg.). About six months after the onset of the adenitis (May 1943) an inflammatory condition of the left eye had developed.

The patient presented himself for examination at the clinic on Jan. 11, 1944, at which time multiple draining sinuses were noted around the neck and in the axillas. Guinea pigs were inoculated with exudate obtained from some of the sinuses, and evidence of tuberculosis was found on examination of the animals. A tuberculin test in which first strength purified protein derivative was used gave a positive result. The sedimentation rate ranged from 6 to 22 mm. per hour (Westergren). A roentgenogram of the chest was normal.

A diagnosis of tuberculous iridocyclitis was made by the consultants in the section on ophthalmology. Administration of promizole was begun on Jan. 14, 1944, with a dose of 16 Gm. daily and was continued for three months. At intermittent intervals thereafter, 500 Gm. of promizole per course was given until November 1944. At that time oral administration of promizole was discontinued and was replaced by topical application of powdered promizole to the ulcers and into the draining sinuses. Topical application was continued until February 1945.

The ulcers and most of the sinuses healed, and the inflammation of the eye subsided by July 1944. A few sinuses persisted in the axillary regions at the time the patient was dismissed from the clinic, in February 1945. Subsequent reports from the patient as late as February 1946 revealed that improvement had been maintained up to that time, although occasionally a new abscess developed around the cervical region. He had gained about 25 pounds (11.3 Kg.).

STREPTOMYCIN

Streptomycin usually was given in doses of approximately 1,000,000 units per day as a streptomycin salt in an aqueous solution. At present 1,000,000 units of streptomycin is referred to as 1 Gm. Approximately 125 mg. was injected intramuscularly every three hours throughout the twenty-four hours. One patient received 2 Gm. daily for a few weeks, but this dose was discontinued because the patient complained of nausea, lassitude and general debility. In general, however, the drug was of low toxicity and was tolerated well by the majority of the patients. Early in the production of streptomycin some inadequately purified materials produced febrile reactions and histamine-like headaches soon after injections, but these reactions were eliminated when purified preparations were made available. The total doses per course of treatment varied from 15 to 128 Gm. In 3 cases in which treatment was given soon after the introduction of streptomycin, the smaller doses per course were given. A relapse occurred within a short time in these cases, and hence it was thought that the smaller total doses per course were inadequate. Some of these patients were given a second course, in which the larger total dose averaged about 60 Gm. Some patients who were treated later received as much as 128 Gm. in a continuous program.

As streptomycin was not always available, it was necessary in some cases to discontinue treatment when our supply was exhausted. Even though we realized the value of larger doses, such as 2 Gm. a day, it was not always possible to give these doses for a long period.

The following reports of 5 cases illustrate the effect of streptomycin in cases of scrofuloderma, tuberculosis miliaris disseminata faciei and tuberculosis cutis colliquativa.

CASE 5.—*Scrofuloderma.*—A white man 60 years of age had begun to have a series of suppurative processes in the lymph nodes in the cervical and submaxillary regions in 1943. Multiple draining sinuses had subsequently developed from these lesions. Efforts at surgical excision had been unsuccessful, and no tendency to healing was observed prior to treatment at the clinic.

The patient's general health had been good. He had lost only 8 pounds (3.6 Kg.). Roentgenologic examination of the chest gave negative results. Inoculation of a guinea pig with material from a cervical abscess gave positive evidence of Myco. tuberculosis.

Treatment with streptomycin was begun in July 1945, and the patient received 21.5 Gm. of streptomycin in five weeks. The course was interrupted briefly because a febrile reaction occurred from impurities from one lot of the drug. The drug was well tolerated after subsequent resumption of treatment with a different lot. At the end of this course of treatment, drainage from the sinuses had stopped and the inflammatory reaction of the abscesses was reduced materially.

A few months later the patient commenced to lose weight. Tuberculous peritonitis developed later, and he died elsewhere eight months after treatment with streptomycin was stopped.

CASE 6.—*Scrofuloderma.*—The patient, a white man 21 years of age, registered at the clinic in October 1945. In March 1943, while he was in military service, cervical adenitis had developed for the first time. One of the nodes had been excised and had been reported to be tuberculous. Subsequently, fluctuation, ulceration and persistent draining sinuses developed. Similar lesions occurred in both axillas in the spring of 1945.

Several smears of the secretion from the draining sinuses made at the clinic were negative for Myco. tuberculosis, but results of inoculations of guinea pigs with material from the same source were positive. Mantoux tests performed elsewhere were reported as giving a positive result.

The patient received the first course of treatment with streptomycin, beginning on Oct. 11, 1945. He received 69.0 Gm. in fifty-six days. In the course of treatment, the circumference of his neck decreased from 40 to 34 cm. and all sinuses stopped draining. Several hard palpable cervical lymph nodes were still present.

On Jan. 1, 1946, three weeks after the patient was dismissed from the clinic, however, ulceration recurred at the former sites, axillary sinuses drained again and another axillary abscess developed. A second course of streptomycin was begun on Jan. 16, 1946, and the total dose for this course was 73.4 Gm. Most of the ulcers healed, but several of the sinuses were patent but dry when the man was dismissed from the clinic, on April 15, 1946. An oral lichen planus, which was not considered relevant to treatment with streptomycin, developed about this time.

CASE 7.—*Scrofuloderma.*—A white woman 70 years old registered at the clinic on Dec. 16, 1945. Suppurating cervical adenitis on the right side had developed in September 1945. The lesion enlarged rapidly and was incised and drained in October 1945. A large draining ulcer resulted at the site of incision and was still present when she came to the clinic.

A roentgenogram of the chest made at the clinic revealed evidence of emphysema. A tuberculin test to first strength purified protein derivative was positive. Res-

of inoculations of guinea pigs with purulent exudate from the surface of the ulcer were positive for Myco. tuberculosis, as was a culture of the same material. A smear of material from the surface of the ulcer revealed acid-fast organisms. A biopsy specimen from the edge of the ulcer revealed caseous tuberculosis.

Treatment with streptomycin was instituted on Dec. 20, 1945 (fig. 2 *a*), and the patient received 85.5 Gm. in eighty-one days. She was dismissed from the clinic on March 12, 1946. At that time the ulcer was about 90 per cent healed. She returned to the clinic in May 1946, and the ulcer was then well healed (fig. 2 *b*).

CASE 8.—*Tuberculosis miliaris disseminata faciei.*—In a white woman 32 years of age tuberculosis miliaris disseminata faciei had developed in 1941. She had no symptoms or evidence of pulmonary disease at that time, but four months later a pulmonary hemorrhage occurred. A moderately advanced lesion was then manifest on roentgenologic examination of the chest. This lesion cleared with care at a sanatorium. The cutaneous lesions, however, had persisted without spontaneous remissions for four years.

On admission to the clinic in 1945, biopsy of a cutaneous lesion was performed and the clinical diagnosis made elsewhere was confirmed. A culture of the gastric contents revealed Myco. tuberculosis, and an apical lesion of pulmonary tuberculosis of minimal extent had reappeared. The sedimentation rate was moderately elevated. An attempt was made to culture the specimen of the skin, but this was unsatisfactory. The results of two inoculations of guinea pigs were negative.

The patient was hospitalized for six months. In this period three courses of streptomycin were administered. A total of 100 Gm. was given. No significant lasting improvement of the cutaneous lesions occurred, although temporary remissions were noted in relation to each of the three courses of treatment. These remissions were followed promptly by relapses when treatment was discontinued. The woman gained 16 pounds (7.3 Kg.), her general health improved and a roentgenogram of the chest revealed clearing of the pulmonary infection. We have minimized the effect of treatment on the cutaneous lesions in view of the tendency for this disease to develop spontaneous remissions.

CASE 9.—*Tuberculosis cutis colliquativa; scrofuloderma.*—A white man 46 years of age came to the clinic in April 1945. Adenopathy had developed in the right supraclavicular region in 1943. A node was excised for biopsy elsewhere and was reported to be a gumma. The incision failed to heal, and soon a crusted ulcer developed. In the following two years similar lesions had developed in the sternal region and on both sides of the neck. Previous to registration the right axillary nodes suppurated and ruptured spontaneously, and a purulent exudate drained through several sinuses. Antisyphilitic treatment had been administered elsewhere and had been ineffective. There had been no tendency to spontaneous improvement.

In the course of examination of the patient at the clinic, smears made with material from the ulcers and cultures of exudate from various ulcers and sinuses revealed acid-fast organisms of the Myco. tuberculosis type. The first strength intracutaneous tuberculin test utilizing purified protein derivative gave a strongly positive reaction. The sedimentation rate was 75 mm. per hour (Westergren). A biopsy specimen from an ulcer revealed an atypical tuberculosis cutis colliquativa.

Administration of streptomycin was begun on April 7, 1945. The patient received only 17.1 Gm. of the drug in forty-four days. All ulcers were essentially healed at the end of the course of treatment, and the patient gained 5 pounds (2.3 Kg.). He was dismissed from the clinic at the end of the course of treatment.

Fig. 2 (case 7). — *Left,* scrofuloderma; *right,* result following administration of 85.5 Gm. of streptomycin in eighty-one days.

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Fig. 3 (case 10). — Lupus vulgaris. *Left*, August 1945; *right*, December 1945; healing of the ulceration after administration of 115 Gm. of streptomycin. A biopsy specimen on Dec. 12, 1945 still shows active tubercles.

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About a month later the ulcers recurred at the former sites and gradually enlarged, so that in four months, after treatment with streptomycin was stopped, they were the same size they had been on the patient's first admission.

A second course of streptomycin was instituted Sept. 30, 1945, and the patient received 31.6 Gm. in thirty-five days. Although this course of treatment was regarded as inadequate, 80 per cent of the ulcers had healed when the patient was obliged to return home and the treatment was discontinued. Subsequent follow-up at a recent date revealed that some ulcers were still present and draining.

PROMIZOLE AND STREPTOMYCIN

In the following 3 cases promizole was given first, and, when results were considered to be unsatisfactory on months of observation, streptomycin was given.

CASE 10.—*Lupus vulgaris.*—The patient, a white woman 48 years old, registered at the clinic in August 1944. She had been found to have tuberculous cervical adenitis in 1930. Cervical adenitis increased and abscesses formed periodically in the following ten years. In 1942 a plaque of infiltrated erythematous dermatitis appeared on the neck. This rapidly progressed in the following two years and extended upward onto the left cheek and lobe of the left ear and downward on the left side of the neck.

In August 1944, the patient presented herself at the clinic, when the large infiltrated plaque just described was observed and the central portion of the plaque was ulcerated and exudative. Diascopy revealed numerous apple jelly nodules. Biopsy revealed that the lesion was typical of lupus vulgaris. An intradermal test with first strength purified protein derivative gave a strongly positive result. The sedimentation rate was 55 to 80 mm. per hour (Westergren). When a guinea pig was inoculated with material from the plaque no gross lesions were seen, but cultures of the spleen of the animal were positive for Myco. tuberculosis. The patient was obese, and her general health was good. The roentgenogram of the chest revealed no abnormalities.

From August to November 1944, the patient received 1,400 Gm. of promizole. The drug was well tolerated but produced no significant improvement in the cutaneous lesions.

When the patient returned to the clinic on Aug. 22, 1945, the lesions had not healed (fig. 3*a*). Treatment with streptomycin was instituted. She was considered to be a suitable candidate for treatment because no tendency to spontaneous improvement had been evident in the observation period of one year. She received 115 Gm. of streptomycin in one hundred and seventeen days. In this period, gradual healing of the ulcerative process occurred and considerable involution of the infiltrative quality was noted (fig. 3*b*). However, biopsy performed at the termination of this course of treatment revealed that typical tubercle formation was still present. This was regarded as an indication of latent activity.

CASE 11.—*Lupus vulgaris.*—A white man 33 years old registered at the clinic. Cervical lymphadenopathy had developed in 1938. Excision of a node from the left side of the neck had resulted in a draining sinus, which had persisted for almost a year. The pathologist had reported that a nonspecific inflammatory reaction was present in the excised node. In 1940 the draining sinus had been excised, and the pathologist had reported that hyperplastic tuberculosis was present in the specimen. A plaque of lupus vulgaris had developed at the site of excision and

gradually had enlarged. Another small plaque developed on the nose in 1942 and one on the scalp in 1943.

In February 1944, when the patient was examined at the clinic, the plaque at the site of excision in 1940 measured 6 by 10 cm. and involved the left side of the face and neck. A biopsy specimen from the lesion on the left cheek revealed the pattern of lupus vulgaris. No acid-fast organisms were discernible on microscopic examination of the tissue or on culture. Results of inoculation of a guinea pig were negative.

The patient's general health was good. A roentgenogram of the chest revealed considerable mediastinal widening, which was attributed to adenopathy. The sedimentation rate was only slightly accelerated. The patient was hoarse, and laryngoscopic examination revealed thickening and injection of both vocal cords.

Treatment with promizole was instituted in February 1944 and was continued intermittently until November 1944. Treatment was interrupted several times because the patient did not tolerate the drug or because he was absent from the clinic. For the most part, however, administration was regular for periods of a month at a time. He took 10 to 16 Gm. per day. In the period of treatment the lesion was thought to have changed, as the erythematous color faded into a fawn color but no significant involution was apparent.

On April 7, 1945, a course of treatment with streptomycin was begun, and a total of 18 Gm. was administered in twenty-four days. During this course of treatment no change was noted in the cutaneous lesions, and no change was noted subsequently. In view of subsequent experience we believe that the patient did not have an adequate amount of treatment.

CASE 12.—*Scrofuloderma.*—A white farmer 62 years old came to the clinic in October 1944. His health had been good until September 1943, when some fluctuating abscesses developed in the sternal region. These were incised, but persistent draining sinuses developed. In the following year similar abscesses and subsequent draining sinuses developed in the axillary and cervical regions. Roentgenologic examination of the chest revealed no evidence of tuberculosis. Results of routine laboratory tests were within normal limits. Acid-fast organisms were demonstrated in a stained smear of exudate from a draining sinus in the sternal region, and in guinea pigs that were inoculated with the secretion from several of the draining sinuses tuberculosis developed. One culture of exudate obtained from the axilla was positive for Myco. tuberculosis.

Treatment was started on Oct. 19, 1944. The patient received 8 Gm. of promizole daily for four months. Some reduction in drainage from the sinuses occurred, but no significant healing took place. Administration of streptomycin was begun on April 24, 1945 and was continued for twenty-eight days. The patient received 17.6 Gm. of this antibiotic agent in this first course. He remained under observation for two months after treatment was stopped. In this period, several residual draining sinuses healed and some reduction in the inflammatory process of the involved regions occurred.

The patient returned on Sept. 12, 1945, three and a half months after the first course of treatment with streptomycin. A large fluctuating abscess had developed in the right axilla. His temperature was 101 F., and he appeared toxemic and weak. He was hospitalized and was given 31 Gm. of streptomycin in fifty days. Although treatment was regarded as incomplete, he gained 18 pounds (8.2 Kg.) and all sinuses had ceased draining and were healing, although the small necrotic ulcerative area persisted in the right axillary region.

Several draining sinuses were reported as still existing on May 5, 1946.

COMMENT

Treatment with promizole offered little encouragement, because of the variation in therapeutic effects in different cases of the same disease. The lesions of erythema induratum healed in case 3 while the patient was taking the drug, but one year and four months after treatment was stopped the ulcerations recurred in a mild form. In 1 case (not reported in detail) presumptive primary inoculation tuberculosis of the cheek which had been present for three months underwent involution rapidly and did not recur. We have observed previously the phenomena of spontaneous involution in primary inoculation tuberculosis, but the involution was not so rapid as in this case. Results of treatment with promizole in cases of lupus vulgaris and of scrofuloderma were for the most part unsatisfactory. In some cases in which promizole was used in treatment of other types of tuberculosis at the clinic, it produced complications, which on occasion required discontinuing its use. Although leukopenia and generalized toxic erythema were rare in these cases, they were the most serious reactions. Headache and gastric discomfort and nausea were fairly common complications. Although these reactions limited the amount of the drug that could be given and occasionally prevented further administration, no serious sequelae occurred. No doubt the continued use of promizole in the presence of these reactions would have produced serious complications.

Streptomycin seemed to offer more encouragement from the beginning, but its therapeutic effects were of short duration in some of the patients in this series of cases, especially those who received relatively small amounts of the drug. The ulcerations and sinuses of the colliquativa and suppurative processes responded most satisfactorily to treatment, and the patients' general condition improved somewhat. The ulcerations and the drainage from the sinuses in case 12 were almost completely healed when the patient left the hospital at the completion of the first course of treatment with 17.6 Gm. of streptomycin, only to recur four months later. In 1 case of lupus vulgaris (case 10), the ulceration healed and infiltration was reduced materially; however, biopsy which was performed at the end of the course of treatment revealed active classic tubercle formation. In case 8, in which tuberculosis miliaris disseminata faciei and active pulmonary tuberculosis were present, the pulmonary lesion involuted during treatment. The patient gained 16 pounds (7.3 Kg.), but the lesions of the face, which improved temporarily, were unchanged after 100 Gm. of streptomycin had been given in six months, during which the patient was in bed. Because these patients were in the hospital, the general improvement and gain in weight should not be attributed entirely to the streptomycin.

Streptomycin produces few reactions but is more toxic than penicillin. Urticaria, headache and local discomfort at the site of injection were

not troublesome in our cases. Vertigo, in the whole series of cases of tuberculosis of various types treated with streptomycin was a common and troublesome reaction, which persisted for several months after treatment. The impurities encountered in some of the earlier preparations of streptomycin produced reactions of a histamine-like type and toxic erythema; however, these impurities are not present in the more recent preparations.

In 3 cases streptomycin was given after promizole had failed to produce any improvement. As yet we have not used streptomycin and promizole at the same time.

CONCLUSIONS

Conclusions are not warranted in an appraisal of promizole and streptomycin in the treatment of cutaneous tuberculosis after such a short experience in a comparatively few cases. We now believe that treatment was inadequate in some of the cases. Because there were no precedents for us to follow in treatment with these drugs, we have felt our way along and have not been without some encouragement. When sufficient quantities of streptomycin are available, we plan to give some patients with cutaneous tuberculosis a minimum of 2 Gm. per day for several months. In the series of patients we treated, those who had scrofuloderma and received the larger doses of streptomycin derived the most benefit. It seems probable that the results of treatment of early primary infections, such as inoculation types of tuberculosis of the skin, may be expected to be better than the results of treatment of long-standing organized processes or extensive id reactions in which few tubercle bacilli are present. A therapeutic parallelism in this regard may exist in early and parenchymatous syphilis. We have not overlooked the possibility that in the patients with sinuses and ulcerations the drugs used might have been effective primarily against the secondary bacterial invaders, but this appears improbable because of the limited range of action of these substances and the failure of other antibacterial agents in similar circumstances.

It appears that streptomycin, although not the ideal agent for the treatment of cutaneous tuberculosis and tuberculids, does offer considerable encouragement because of its therapeutic efficacy in guinea pigs inoculated with tuberculosis and because of the varying degrees of improvement in human beings. The therapeutic trials should be continued, and more should be done to stimulate further laboratory investigations for a therapeutic agent that will have a more intense specific action against tubercle bacilli in human beings.

ELEPHANTIASIS NEUROMATOSA

A Manifestation of von Recklinghausen's Disease

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VON RECKLINGHAUSEN'S disease, or multiple neurofibromatosis, is a form of congenital dysplasia manifested by developmental changes in the nervous system, the skin, the bones, and the muscle. The disease is frequently familial and may be associated with endocrine imbalance, muscle weakness, or paralysis due to involvement of the cerebrospinal system.

Cutaneous lesions may be divided into three general types: (1) café-au-lait spots associated with freckles or hyperpigmentation; (2) molluscum fibrosum—superficial dermal tumors caused by proliferation of the connective tissue of peripheral nerve sheaths, and (3) subcutaneous neurofibroma, distorting the skin contour.

Nervous involvement is due largely to the dominant tissue of the nerve sheath—neurectodermal Schwannian syncytium.[1] Although there is a controversy as to the origin of the connective tissue, the majority opinion indicates that the Schwann sheath cells are the source of the connective tissue, causing neurofibrotic growths which may involve one nerve, a sheath or a plexus of nerves, or may be generalized to include cranial, spinal and sympathetic nerves. It should be mentioned that there is a tendency to sarcomatous change in the neurofibrotic tumors found in von Recklinghausen's disease.[2] Cumbersome lesions, there-

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1. (*a*) Masson, P.: Histogénèse des neurofibromes cutanés diffus, Bull. Soc. franç. de dermat. et syph. **42**:1278, 1935. (*b*) Masson, P.: Tumeurs encapsulées et bénignes des nerfs, Rev. canad. de biol. **1**:209, 1942. (*c*) Masson, P.: Recklinghausen's Neurofibromatosis, Sensory Neuromas and Motor Neuromas, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 2, p. 739. (*d*) Stout, A. P.: Tumors of Peripheral Nerves, New England J. Med. **225**:314, 1941. (*e*) Murray, H. R.; Stout, A. P., and Bradley, C. F.: Schwann Cell Versus Fibroblasts as the Origin of the Specific Nerve Sheath Tumor, Am. J. Path. **16**:41, 1940. (*f*) Geschickter, C. F.: Tumors of the Peripheral Nerves, Am. J. Cancer **25**:377, 1935.

(Footnotes continued on next page)

fore, should have complete excision, for new lesions contiguous with an old lesion, or even in a new location, may undergo sarcomatous change.

Skeletal changes frequently associated with von Recklinghausen's disease have been found most commonly to be scoliosis,[3] abnormalities of excess [4] and deficient growth.[5] Each of these changes is sometimes seen in the same case. Irregularities of outline of the shafts of the long bone, including changes which appear as subperiosteal bone cysts (in reality, neurofibromatosis of the periosteal nerve with outer layer of calcification due to periosteal reaction), represent other changes in the skeletal system which are sometimes associated with this disease.[6] All the bone changes observed could be explained on the basis of tumor tissue characteristic of neurofibroma involving the bone by involvement of the periosteal nerve, the lymphatics and the epiphysial cartilage. Neurofibromatous involvement of the marrow cavity has been recorded.[7]

Endocrine changes sometimes associated with multiple neurofibromatosis are menstrual abnormalities, acromegaly, cretinism, delayed or incomplete sexual development, myxedema, tetany, Addison's disease

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2. (*a*) Geschickter.[1f] (*b*) Lewis, D., and Hart, D.: Tumors of Peripheral Nerves, Ann. Surg. **92**:961, 1930. (*c*) Charache, H.: Multiple Neurofibroma with Sarcomatous Transformation and Skeletal Involvement, Arch. Dermat. & Syph. **40**:185 (Aug.) 1939. (*d*) Miller, A.: Neurofibromatosis with Reference to Skeletal Changes, Compression Myelitis and Malignant Degeneration, Arch. Surg. **32**:109 (Jan.) 1936. (*e*) Lewis, D.: Elephantiasis Nervorum, Ann. Surg. **93**:209, 1931.

3. (*a*) Miller.[2d] (*b*) Brooks, B., and Lehman, E. P.: Bone Changes in Recklinghausen's Neurofibromatosis, Surg., Gynec. & Obst. **38**:587, 1924. (*c*) Lehman, E. P.: Recklinghausen's Neurofibromatosis and the Skeleton: A Plea for Complete Study of Disease, Arch. Dermat. & Syph. **14**:178 (Aug.) 1926. (*d*) Gould, E. P.: The Bone Changes Occurring in von Recklinghausen's Disease, Quart. J. Med. **11**:221, 1918. (*e*) Stalmann, A.: Nerven- Haut- und Knochenveränderungen bei der Neurofibromatosis Recklinghausen und ihre entstehungsgeschichtlichen Zusammenhange, Virchows Arch. f. path. Anat. **289**:96, 1933. (*f*) Diasio, F. A.: Elephantiasis Neuromatosa (von Recklinghausen's Disease), Urol. & Cutan. Rev. **36**:104, 1932. (*g*) Brunner, W.: Beitrag zur Elephantiasis neuromatodes, Deutsche Ztschr. f. Chir. **246**:751, 1936. (*h*) Heusch, K.: Ueber die Beziehungen des Sympathicus zur Neurofibromatose und dem partiellen Riesenwuchs, Virchows Arch. f. path. Anat. **255**:71, 1925. (*i*) Jordan, M.: Pathologisch-anatomische Beiträge zur Elephantiasis congenita, Beitr. z. path. Anat. u. z. allg. Path. **8**:71, 1890.

4. (*a*) Stalmann.[3e] (*b*) Brunner.[3g] (*c*) Heusch.[3h] (*d*) Jordan.[3i] (*e*) Spittel, R. L., and Fernando, S. E.: Elephantiasis Neuromatosa, Brit. M. J. **1**: 596, 1929.

5. Brooks.[3b] Stalmann.[3e] Heusch.[3h] Jordan.[3i]

6. Brooks.[3b] Stalmann.[3e] Spittel and Fernando.[4e]

7. Friedman, M. M.: Neurofibromatosis of Bone, Am. J. Roentgenol. **51**: 623, 1944.

and a diabetic blood sugar curve.[8] Thus, multiple neurofibromatosis may manifest itself in many ways. One of the rarer and more interesting types seen in conjunction with von Recklinghausen's disease is that of elephantism neuromatosa of Virchow—a fibromatosis of cutaneous nerves, merging into a diffuse overgrowth of subcutaneous tissue and skin, giving an elephantiasis, or enlargement, of the part affected.[9] The overlying skin may be normal but frequently is thickened and pigmented. At times, thickened or coiled nerves may be palpated within. Such an enlargement often appears in childhood.[10] It is usually progressive and disfiguring and is sometimes incapacitating and painful. The frequently associated familial tendency and bone and endocrine changes are also seen with this variation.[11] Of course, in multiple neurofibromatosis there may be any gradation of tumor, varying from the small cutaneous elevations to the huge tumors involving an entire lower extremity, causing extreme deformity and showing many associated bone changes. The dividing or differentiating line between neurofibromatosis, plexiform neurofibroma and elephantiasis neuromatosa is difficult to determine. Our 2 cases represent the large lesions of the elephantiasis neuromatosa group.

The typical history is that of a child (one of whose parents had a history of von Recklinghausen's disease) presenting signs of generalized neurofibromatosis which has slowly progressed from a small skin nodule into a mass. This mass is most frequently located around the neck or on the extremities.[12] In 8 of the 42 cases reported by Bruns,[13] a mass developed in the neck.

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8. (*a*) Charache.[2e] (*b*) Brunner.[3g] (*c*) Rosenthal, D. B., and Willis, R. A.: The Association of Chromaffin Tumors with Neurofibromatosis, J. Path. & Bact. **42**:599, 1936. (*d*) Tucker, B. R.: Von Recklinghausen's Disease with Especial Consideration of Endocrine Connection, Arch. Neurol. & Psychiat. **11**:308 (March) 1924. (*e*) Levin, O. L.: Von Recklinghausen's Disease: Its Relation to the Endocrine System, Arch. Dermat. & Syph. **4**:303 (Sept.) 1921. (*f*) Louste; Caillau, and Darquier: Syndrome de Recklinghausen et acromégalie, Bull. Soc. franç. de dermat. et syph. **33**:54, 1925.

9. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1863, vol. 1; cited by Jordan.[3l]

10. (*a*) Brooks.[3b] (*b*) Heusch.[3h] (*c*) Jordan.[3l] (*d*) Spittel and Fernand.[4e] (*e*) Corsi, H.: Rare Type of von Recklinghausen's Disease Proc. Roy. Soc. Med. **25**:1739, 1932.

11. (*a*) Diasio.[3f] (*b*) Heusch.[3h] (*c*) Jordan.[3l] (*d*) Spittel and Fernand.[4e] (*e*) Anzinger, F. P.: Congenital Plexiform Neurofibromas and Elephantiasis Neuromatosa of Right Arm and Neck (von Recklinghausen's Disease): Supplementary Report, J.A.M.A. **96**:1381 (April 25) 1931.

12. (*a*) Diasio.[3f] (*b*) Brunner.[3g] (*c*) Heusch.[3h] (*d*) Jordan.[3l] (*e*) Spittel and Fernando.[4e] (*f*) Corsi.[10e] (*g*) Anzinger.[11e] (*h*) Härtel, F.: Fall von risen-

(Footnotes continued on next page)

The common signs and symptoms are pain and/or the presence of a deforming, incapacitating mass. Bone and endocrine changes frequently occur, possibly because of the widespread and extensive form of multiple neurofibromas present.

Evaluation and treatment consist of a complete skeletal roentgenologic examination, an endocrine study (including a study of blood sugar, alkaline and acid phosphatase, chlorides, etc.), followed, if possible, by extensive removal of the affected part, as these lesions tend toward

Fig. 1 (case 1).—*A*, note lobulated mass hanging from the neck down over the wall of the chest. *B*, clinical photograph taken four and one-half years after the operation.

sarcomatous change and recurrence.[14] In 1 case cited in the literature a sarcoma developed in the region of the breast three years after removal of an elephantiasis lesion of the arm.[12h]

The following 2 cases were seen at the Ellis Fischel State Cancer Hospital.

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hafter Lappenelephantiasis bei einer Japanerin, Deutsche Ztschr. f. Chir. **208**:423, 1928.

13. Bruns, P.: Ueber das Rankenneurom, Beitr. z. klin. Chir. **8**:1, 1891.
14. Brunner.[3g] Härtel.[12h]

REPORT OF CASES

CASE 1.—G. E., a 40 year old man, entered the hospital on Feb. 7, 1941, complaining of redundant, nonpainful tumors of the neck, the chest and the scalp since birth. The tumors had grown with a rate corresponding to the patient's growth. Approximately three years before the patient's admission the tumors began to grow more rapidly. The patient's mother had von Recklinghausen's disease.

Physical examination showed a soft, pedunculated, freely movable mass 8 cm. in diameter on the left side of the neck, beginning at the upper part of the nucha and extending down to the level of the fourth cervical vertebra. There was a redundant soft pedunculated mass, apparently arising from subcutaneous tissue, extending from the left mastoid process along the left mandible to the left nipple

Fig. 2 (case 1).—Roentgenologic view of the cervical spine, showing excessive deformity.

(fig. 1 *A*). This was covered with brown, atrophic, excoriated, reddened skin. There were several areas over 1 cm. in diameter on the skin of the wall of the chest which had the typical café-au-lait appearance. In addition to the primary lesion, this patient had several congenital anomalies: There was a severe deformity of the cervical vertebrae with posterior bowing and fusion; the left clavicle was bowed anteriorly with overriding of the opposite pieces, and the left leg was bowed anteriorly and laterally, with flattening of the tibia in the anterior-posterior diameter. This deformity had been present since birth. Examination of the skin over the rest of the body revealed several café-au-lait spots and molluscum fibrosum on the thorax and the abdomen. Over the left rectus muscle there was a tumor measuring 2 cm. which was similar in consistency to the large one

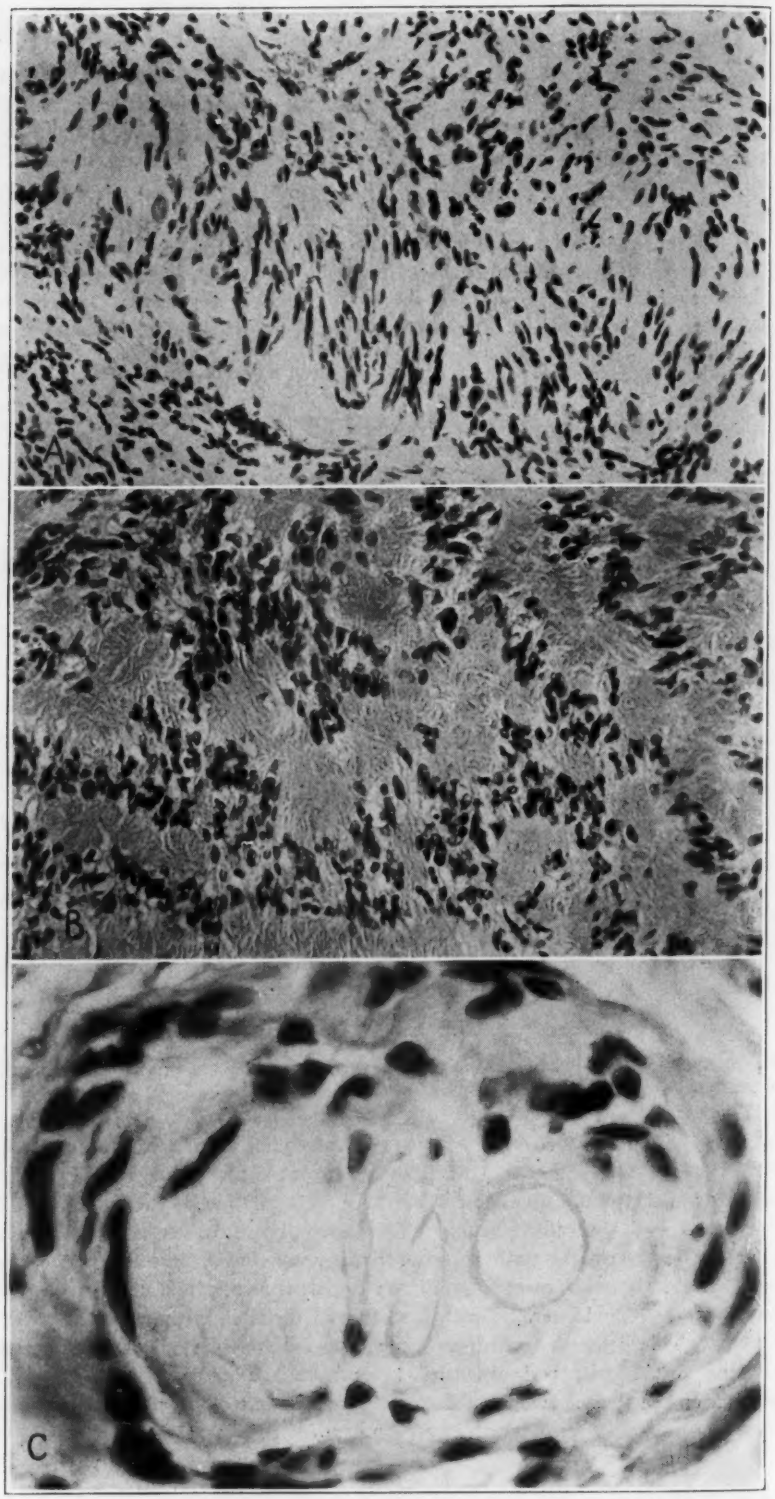

Figure 3

(See legends on opposite page)

previously described. There was also a tumor 0.5 cm. in diameter over the right scapula.

Roentgenograms revealed a multiple soft tissue tumefaction of the chest, the left shoulder girdle and the supraclavicular and infraclavicular regions; asymmetry of the rib cage, deformity of the cervical column with associated arthritic changes, underdevelopment of the first and second cervical vertebrae, developmental changes of the left clavicle, apparently secondary to the tumors of the left shoulder girdle, and developmental deformity of both bones of the left leg. Blood count and urinalysis were within normal limits. A serologic test for syphilis elicited a negative reaction.

It was decided that this lesion could best be treated by a two stage excision. The mass in the neck and in the wall of the chest was excised on February 12, and a split thickness graft was applied. Twenty days later the mass in the scalp and the neck was excised and the tumor was found to extend to the foramen magnum. A scar subsequently developed in the midline of the neck, but this was corrected with a plastic procedure. There was no evidence of recurrence four and a half years after this treatment.

Pathologic Examination.—The surface of the specimen had an elephant hide appearance, and in a few areas the skin was thrown into folds and wrinkles. On cut section the tumor was gray-white. It cut with difficulty and was homogeneous throughout, with no areas of hemorrhage or necrosis. Microscopically, the sections showed areas characteristic of the loose-textured arrangement of Schwannian cells. In other zones cells had more deeply stained nuclei and tended to be larger and somewhat irregular. The tumor invaded the muscle, separating its bundles. There were areas where the arrangement of cells suggested strongly the histologic pattern which one sees in neurilemmoma (fig. 3 *A* and *B*). There were also structures which caricatured the Wagner-Meissner tactile corpuscles (fig. 3 *C*). A questionable pacinian body was observed.

Microscopic Diagnosis.—The diagnosis on the basis of microscopic examination was elephantiasis neuromatosa.

The clinical course and pathologic picture were typical of elephantiasis neuromatosa, a manifestation of von Recklinghausen's disease. The associated congenital bony deformities were those occasionally seen in this disease.

Case 2.—O. B., a 22 year old man, entered the hospital Nov. 15, 1940, with the chief complaint of soft masses under the right arm and under the right pectoral region which had been present for ten years. These small, soft masses grew progressively larger but caused no pain. A biopsy was performed four years previous to his admission, and soon afterward pain appeared in the right arm.

Physical examination revealed a lobulated, pedunculated, movable mass, the base of which was attached to the right pectoral region of the chest wall (fig. 4).

Explanation of Plate.

Fig. 3 (case 1).—*A*, photomicrograph of an area in the tumor showing resemblance to the neurilemmoma in *B*. *B*, photomicrograph of a typical neurilemmoma with palisading and characteristic arrangement. Moderate enlargement. *C*, photomicrograph (high power) of a structure resembling a Wagner-Meissner tactile corpuscle.

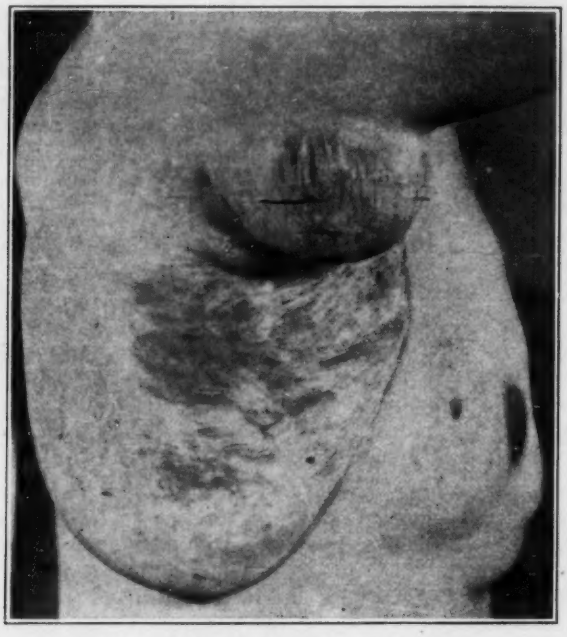

Fig. 4 (case 2).—Clinical photograph of soft pendulous mass in the axilla. Note pigmentation of the tumor and the café-au-lait spot near the nipple.

Fig. 5 (case 2).—Gross photograph of large nodular tumor mass with wrinkled skin. The finger-like processes close to the ruler represent the tumor which extended between the ribs.

The underlying skin was gray-white and nodular to palpation. There were multiple areas of light brown pigmentation scattered over the skin of the arms.

The clinical diagnosis was elephantiasis neuromatosa.

On November 20 an excision of the lesion was performed. At the time of operation it was found that the lesion extended into the uppermost part of the axilla and had digitations extending between the ribs in the third and fourth interspaces, where it appeared to arise from the intercostal nerves and extend back to the vertebral column posteriorly. The fourth rib was so extensively surrounded that it had to be resected. A radical axillary dissection was also performed. The large resultant defect was covered with split thickness graft from the thigh. The operative course was uneventful, and a postoperative roentgenologic examination revealed minimal curvature of the dorsal vertebral column, with convexity to the right. There was slight increase in density of the vertebrae, hypertrophic arthritis and a minimal amount of demineralization of the bone. Subsequent clinical visits and follow-up revealed no new enlargement of any of the remaining neurofibromas, and four and a half years after operation there was no evidence of disability or of recurrence.

Pathologic Examination.—Examination of the specimen revealed firm, poorly defined nodularities palpable underneath the skin. Cut sections showed nodular, gray-white, firm tissue with multiple areas of necrosis. There were finger-tip-like processes which were identified as portions of the tumor which penetrated the costal interspaces. The rib was not grossly or microscopically invaded by the tumor (fig. 5). Microscopically, the changes in this tumor were identical with those found in the previous case.

This case of elephantiasis neuromatosa extensively involved the chest wall and the axilla. It closely resembled the case of Pomorski cited by Bruns,[13] in which the tumor arose from intercostal nerves and extended into the pleural cavity. It is unfortunate that no preoperative roentgenograms were taken, for they might have given indirect evidence of growth of the tumor between the ribs.

SUMMARY

Two patients with typical, rather extensive elephantiasis neuromatosa with secondary bone changes were treated by radical surgical intervention.

DYSKERATOSIS CONGENITA WITH PIGMENTATION, DYSTROPHIA UNGUIUM AND LEUKOPLAKIA ORIS

Patient with Evidence Suggestive of Addison's Disease

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IN A PREVIOUS article [1] 2 brothers were described who had the main features of the syndrome named by Cole and associates. Of considerable importance was the pronounced improvement in the leukokeratotic patches of the mucous membrane of the mouth and tongue of the older brother, J. W., following medication for several weeks with testosterone propionate. In this paper I am reporting the findings in the patient J. W. of the various tests and examinations and the results of treatments with adrenocortical hormones, all of which are suggestive of the presence of associated Addison's disease. This is a part of the investigative work now being carried on by Dr. Fred Wise and myself, with the view of collecting data on the presence of pathologic changes in the adrenal glands in various chronic and resistant dermatologic diseases, as has already been reported by Garb and Wise in a case of mycosis fungoides with bullous lesions.[2] The following description is a brief report of the 2 brothers.

REPORT OF A CASE

J. W., an American-born Jew, had hyperpigmented and depigmented patches on the trunk and extremities. The patches were arrayed in a fine network enclosing normal areas of skin. The skin was dry. The finger nails and toe nails were dystrophic, the finger nails being either wanting or reduced to thin remnants. There were leukokeratotic patches on the buccal mucosa on the left side and on the dorsal surface of the tongue. The teeth were decayed, and many were missing. He had ulcerations in the commissures of the lips. There was an

From the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University College of Physicians and Surgeons, service of Dr. Fred Wise.

1. Garb, J., and Rubin, G.: Dyskeratosis Congenita with Pigmentation, Dystrophia Unguium and Leukoplakia Oris (Cole and Others): Report of the Cases of Two Brothers, with Improvement in the Leukoplakic Patches in One with Androgenic Medication, Arch. Dermat. & Syph. **50**:191 (Sept.) 1944.

2. (*a*) Garb, J., and Wise, F.: Mycosis Fungoides with Bullous Lesions: Report of a Case Resistant to Roentgen and Arsenical Therapy; Effects of Empiric Therapy, Partly Based on Laboratory Investigations, Arch. Dermat. & Syph. **48**:359 (Oct.) 1943. (*b*) Garb, J.: Mycosis Fungoides with Bullous Lesions: Special Tests and Laboratory Data Indicating Adrenal Insufficiency, ibid. **49**:315 (May) 1944.

associated atrophy of the dorsal surfaces of the hands, resembling acrodermatitis chronica atrophicans. The patient was mentally retarded, underweight and physically weak. There was tearing of the eyes due to closure of the tear ducts. On the skin about the nails and on the extremities he had recurrent infections, which were slow to heal.

The younger brother showed similar anomalies except that they developed later in life and were of a milder form.

Routine and special laboratory tests[1] were performed, which have no particular significance for the subject herein discussed except the hemogram taken on Feb. 2, 1943, which is here again recorded. It showed 11.5 Gm. of hemoglobin per hundred cubic centimeters of blood and 3,480,000 erythrocytes and 6,400 leukocytes per cubic millimeter. The differential count showed 39 polymorphonuclear neutrophils, 2 eosinophils, 8 monocytes, 40 lymphocytes and 11 band neutrophils per hundred cells.

Other laboratory data not previously reported are as follows: The color index on Feb. 2, 1943 was 1.2 (normal 0.9 to 1.0) and the volume index 1.7 (normal 0.85 to 1.15). On April 27, 1943 the hemogram showed 50 polymorphonuclear

TABLE 1.—*Chemical Observation on the Blood*

Date	Specimen Examined	Constituents (Normal Range in Parentheses)	Amount, per 100 Cc.
2/25/43	Serum	Proteins:	
		Total (6 to 8 Gm.)	5.0 Gm.
		Albumin (4 to 5 Gm.)	3.7 Gm.
		Globulin (2 to 3 Gm.)	1.3 Gm.
		Ratio (1.6 to 2:1)	2.8:1%
2/25/43	Whole blood	Ratio of urea nitrogen to non-protein nitrogen (35:45)	40%
2/25/43	Serum	Phosphates, inorganic (adults 3.5 to 4.0)	3.4 mg.
3/19/43	Serum	Phosphatase activity (alkaline) (3 to 5)	2.6 (Bodansky units)
2/25/43	Serum	Calcium: Total (9.6 to 11)	11.4 mg.
2/25/43	Serum	Ionized (4.8 to 6.3)	6.1 mg.
2/25/43	Serum	Cholesterol (160 to 230) (lipid partition otherwise normal)	270.0 mg.

leukocytes, 42 lymphocytes and 8 monocytes. On Jan. 11, 1944 the erythrocyte count was 3,500,000; hemoglobin content, 11.5 Gm. (80.7 per cent), and leukocyte count, 7,350, with 27 polymorphonuclear neutrophils, 57 lymphocytes and 13 band neutrophils. The color index was 0.98 and the volume index 1.2. The sedimentation rate was 20 mm. per hour (maximum in men 10 mm. per hour, by the Westergren method). The dextrose tolerance test gave a flattened curve. The blood sugar on a fasting stomach was 65 mg. After the ingestion of 100 Gm. of dextrose, the half hour and five hourly samples contained respectively 85, 80, 60, 65, 65 and 55 mg. per hundred cubic centimeters of whole blood. The urine did not contain sugar. The results of the determination of blood volume for plasma and whole blood were within normal limits. The plasma volume was 49 cc. per kilogram (normal 49 to 55) and the whole blood 90 cc. per kilogram (normal 72 to 100). The viscosity of the whole blood was 7.4 units (normal 4.4 to 5.5).

Two biopsy specimens from a hyperpigmented area showed poikiloderma-like changes. A biopsy specimen of the lesion of the mouth showed leukoplakia.

Laboratory data are given in the tables to facilitate reading and interpretation.

The patient was hospitalized at the New York Post-Graduate Hospital from March 17 to March 24, 1943 for the purpose of having the Robinson, Power and Kepler [3] procedures performed and other special tests done which were needed to furnish additional evidence of possible deficiency or malfunction in the secretions of the adrenal gland as suggested by the clinical signs and symptoms.

TABLE 2.—*Determination of Vitamin C Content in the Blood and Urine*

Date	Specimen Examined	Constituents	Amount, per 100 Cc.
3/19/43	Blood plasma	Vitamin C (0.7 to 1.4 mg.)	0.8 mg.
3/23/43	Blood plasma	Vitamin C (0.7 to 1.4 mg.)	0.7 mg.
6/17/43	Blood plasma	Vitamin C (0.7 to 1.4 mg.)	0.4 mg.
6/17/43	Urine	Vitamin C saturation test (urine excretion after injection of 1 Gm. of vitamin C intravenously)	
		1½ hr.....211 mg. per 210 cc.	
		3½ hr.....138 mg. per 150 cc.	
		5 hr. (over 450 mg.).....349 mg. per 360 cc.	
		Saturation index (over 500).....429 mg. in 24 hr.	

Robinson, Power and Kepler Tests.—The urine voided at 10:30 p. m. on March 25, 1943, was discarded. The urine voided later, up to and including 7:30 a. m., measured 219 cc., and the largest specimen of urine voided during the day yielded 217 cc. Chemical examination revealed 960 mg. of chlorides and 1,022 mg. of urea nitrogen in the urine and 595 mg. of chlorides and 17 mg.

TABLE 3.—*Special Chemical Observations on the Urine*

Date	Specimen Examined	Constituents	Amounts, per 100 Cc.	Amounts, per Volume
3/19/43	Urine	Creatinine and creatine	0.30 Gm.	1.93 Gm.
		Creatinine	0.26 Gm.	1.67 Gm.
		Creatine	0.04 Gm.	0.26 Gm.
3/19/43	Urine	17-ketosteroids (8 to 23 mg.) 6.5 mg. (in 643 cc. of urine voided in 24 hr.)		
		(in 1,160 cc. of urine voided in 24 hr.)		

of urea nitrogen in the blood plasma. By substitution of these figures in the following formula, which is used for Addison's disease:

$$A = \frac{\text{Urea in urine (mg./100 cc.)}}{\text{Urea in plasma (mg./100 cc.)}} \times \frac{\text{Chloride in plasma (mg./100 cc.)}}{\text{Chloride in urine (mg./100 cc.)}} \times \frac{\text{Volume of day urine (cc.)}}{\text{Volume of night urine (cc.)}}$$

the equation figure of 36.9 is obtained, the significance of which is discussed later.

The daily temperature in the hospital per os ranged from normal to 96.5 F.

Scout films of the abdomen for possible changes in the suprarenal region, taken by Dr. William H. Meyer, "showed no abnormality of the denser organs. The left kidney appeared a shade larger than the right. They were otherwise of normal contour and illumination. There were no abnormal calcifications."

Fractional Gastric Analysis (Jan. 26, 1944).—A fasting specimen was first taken. A pint (0.5 liter) of thin gruel was then given, and specimens were

3. Robinson, F. J.; Power, M. H., and Kepler, E. J.: Two New Procedures to Assist in Recognition and Exclusion of Addison's Disease, Proc. Staff Meet., Mayo Clin. **16**:577 (Sept. 10) 1941.

obtained twenty and forty minutes later. Histamine phosphate, 0.5 cc. of 1 to 1,000 solution, was then injected subcutaneously, and samples were collected at the end of twenty and forty minutes. Results obtained are given in table 4.

Determination of blood pressure was taken on several occasions with the patient in the recumbent and upright positions, with results given in table 5.

Follow-up of the Patient J. W. Since March 1944.—The patient continued to take dried yeast in tablespoon doses three times a day after meals for eight

TABLE 4.—*Results of Fractional Gastric Analysis*

Specimen	Milliequivalents of Cl per Liter: Free HCl	Total Acidity	Color	Mucus	Lactic Acid
Fasting	Negative	39	Gray-white	Mucoid	Negative
one pint (0.5 liter) thin gruel taken:					
20 min. after	Negative	10	Gray-white	Fluid	Negative
40 min. after	Negative	10	Gray-white	Fluid	Negative
Histamine phosphate injected:					
20 min. after	Faint trace	18	Gray-white	Fluid	Negative
40 min. after	20 degrees	49	Gray-white	Fluid	Negative

months; thus sufficient time was allowed for any definite manifestation of regression of the leukoplakic patches that might result from the ingestion of such large doses of vitamin B complex.[4] There was, however, no noticeable change during this prolonged period of trial in the lesions, which had partly recurred following the discontinuance of the use of the androgenic medicament in December 1943.[5] On Jan. 18, 1945 oral administration of adrenal cortical extract[6] was prescribed instead of the dried yeast, 1 tablet to be taken three

TABLE 5.—*Rowntree or Schellong Tests*[14]

Date	Right Arm: Horizontal Position	Right Arm: Upright Position	Left Arm: Horizontal Position	Left Arm: Upright Position
1/ 1/43	120/60	110/60	120/60	110/60
1/22/44	100/20	110/60	100/20	110/60
1/25/44	100/40	110/50	105/50	120/60
1/18/45	100/60	100/40	100/60	110/60
4/12/45	100/50	120/60	110/70	120/60

times a day before meals. After six weeks 2 tablets of adrenal cortical extract were given three times a day. Photographs were taken on Jan. 18 and on April 26, 1945. During these three months the patient gained only 1 Kg. in

4. Martin, H., and Koop, E. C.: The Precancerous Mouth Lesions of Avitaminosis B, Am. J. Surg. **57**:207 (Aug.) 1942.

5. Garb and Rubin,[1] p. 195.

6. The adrenal cortical extract was Cortalex, The Upjohn Company, Kalamazoo, Mich. Each tablet presents the physiologically active adrenal cortical hormone contained in 5 Gm. of fresh adrenal gland, together with 15 mg. of ascorbic acid.

weight. He stated, however, that he felt more vigorous. He did not tire so easily as formerly. His appetite was still poor, but it was improving. There was a good change in the blood pressure readings (table 5). The leukoplakic patches showed definite signs of regression on the middle and lower borders of the left cheek.

COMMENT

Interpretation of Laboratory Data.—The hemograms showed an increase in the band neutrophils, or stab cells of Schilling, which are immature or nonsegmented cells. This is a shift to the left occurring in chronic infections.[7] The increased sedimentation rate of 20 mm. per hour is likewise indicative of a chronic infection.[8] The total protein content in the blood serum of only 5 Gm. (table 1) corresponds with its diminution in malnutrition.[9] The rise in the blood cholesterol level to 270 mg. per hundred cubic centimeters was anticipated, as hypercholesteremia occurs among other diseases in various degenerative conditions[10]; so was the increase in the twenty-four hour urinary excretion of creatinine to 1.67 Gm. (normal, 1.25 Gm.), as shown in table 3, expected, as larger amounts of creatinine are eliminated in the urine in wasting diseases because of tissue catabolism.[11]

Evidence Suggestive of Adrenal Insufficiency.—The following evidence is indicative of hypofunction of the adrenals notwithstanding the normal endocrinologic findings[1] and the high equation figure of 36.9, which according to Robinson and colleagues[12] would be interpreted as indication against the presence of Addison's disease.

1. The patient had complaints of asthenia, loss of weight, chronic constipation, depression of the sexual function and glossitis.

2. There were gastrointestinal symptoms manifested by attacks of vomiting, which were at times severe and accompanied with the presence of blood in the vomitus. Gastrointestinal disturbances occur sometimes in Addison's disease and when severe may simulate a gastric crisis.[13]

3. The Rowntree or Schellong test[14] (table 5) elicited a positive reaction. The blood pressure readings on Jan. 1, 1943 were lower by 10 degrees in both arms in the upright position as compared with those

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7. Kolmer, J. A.: Clinical Diagnosis by Laboratory Examination, New York, D. Appleton-Century Company, Inc., 1943, p. 30.

8. Kolmer,[7] p. 21.

9. Kracke, R. R., and Parker, F. P.: A Textbook of Clinical Pathology, Baltimore, Williams & Wilkins Company, 1940, p. 317.

10. Kracke and Parker,[9] p. 294.

11. Kolmer,[7] p. 73.

12. Robinson, Power and Kepler,[8] p. 580.

13. Harrop, G. A.: The Adrenal Glands, in Tice, F.: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1921, vol. 8, p. 322.

14. Wolf, W.: Endocrinology in Modern Practice, ed. 2, Philadelphia, W. B. Saunders Company, 1939, p. 937.

in the horizontal posture. On Jan. 22 and 25, 1944 the readings were higher in both arms in the upright position. This improvement and the fact that the patient felt generally better and stronger should justifiably be attributed to the use of testosterone propionate.

4. There was pigmentation, which was generalized, more pronounced and deepest in the areas exposed to light, as the face and neck, with the bathing trunk area unaffected, and there were numerous vitiliginous patches on the face, neck and trunk, which are commonly seen in Addison's disease.[15]

5. Results of examination of the creatine and creatinine content in the urine were indicative of renal insufficiency. The combined creatine and creatinine value was 0.30 Gm., and the creatine content was 0.04 Gm., or 13.3 per cent, in a twenty-four hour volume of urine (table 3). This, according to Steinach and his co-workers,[16] points to a deficiency in the secretion of androgens, as such a hormonal deficiency is present if the amount of creatine in the urine is 10 per cent or more of the combined value of the creatine and creatinine. This is corroborated by the low 17-ketosteroid content of 6.5 mg. (table 3). Since this hormone is in males an index of the combined activity of the adrenals and the gonads, the low 17-ketosteroid content could reasonably be attributed to deficiency in both these ductless glands.

6. A vitamin C deficiency was present (June 17, 1943; table 2). This may indicate a depletion of vitamin C in the adrenal cortex, since the proper function of this gland depends on the large amount of ascorbic acid [17] which it normally stores.

7. The flat sugar tolerance curve indicated renal insufficiency. Eppinger and Rudinger [18] have shown that patients with Addison's disease (hypoadrenalism) have an increased tolerance for sugar.

8. There was a rise in viscosity of the whole blood to 7.4 units. This is increased in Addison's disease due to anhydremia.

9. Examination of the gastric content showed achlorhydria even after the test meal and yielded only a trace of hydrochloric acid twenty minutes after stimulation with histamine (table 4). A low gastric acidity or complete anacidity is commonly found in Addison's disease.[19]

15. Harrop,[13] p. 320.

16. Steinach, E.; Kun, H., and Peczenik, O.: Diagnostischer Test für hormonbedingte Störungen der männlichen Sexualfunktion und seine klinische Anwendung, Wien. klin. Wchnschr. **49**:388, 1936; cited by Feldman, S.; Pollock, J., and Abarbanel, A. R.: Treatment of Senile Pruritus with Androgens and Estrogens, Arch. Dermat. & Syph. **46**:113 (July) 1942.

17. Harrop,[13] p. 307.

18. Eppinger, H., and Rudinger, K., cited by Falta, W.: Erkrankungen der Blutdrüsen, Berlin, Julius Springer, 1913, p. 276.

19. Harrop,[13] p. 322.

10. The results of the hemograms indicated adrenal insufficiency. Kracke and Parker [20] stated that the blood in Addison's disease is usually normal but that a macrocytic anemia may occasionally be present. The hemograms had the features of moderate macrocytic anemia. This is shown by the lowered erythrocyte count of 3,500,000, the hemoglobin content of 11.5 Gm., the relative lymphocytosis (27 polymorphonuclear neutrophils and 57 lymphocytes) with 13 band neutrophils, the color index of 1.2 and the volume index, which was 1.7 on Feb. 23, 1943 and 1.2 on Jan. 11, 1944.

11. There was an increased urinary excretion of creatine, which occurs in wasting conditions and disorders of the muscles and is present in Addison's disease when the "adynamia is severe." [19] Creatine is not normally found in the urine of normal men, as it is converted into creatinine before excretion, but it may occur in them in amounts up to 196 mg. per twenty-four hours.[11] The patient had the high creatine excretion of 1.93 Gm. per twenty-four hours, or 0.04 Gm. per hundred cubic centimeters of urine.

12. There was response to therapy, as shown by the regression of the bullae of the mouth within three weeks after the administration of testosterone propionate. This may justifiably be attributed to the direct beneficial action of the androgens on the kidneys and adrenal glands similar to the action of the adrenocortical hormones on the latter in Addison's disease.[21]

13. The partial recurrence of the leukoplakic patches within three months following the discontinuance of administration of testosterone propionate,[5] the improvement in the general well-being of the patient, the change for the better in the blood pressure readings of April 12 over those of Feb. 1, 1945 (table 5) and the regression of the leukoplakic patches in the center and lower borders of the oral mucosa following four months of medication with adrenal cortical extract add still further valuable evidence of cortical disturbance.

The low 17-ketosteroid content, the increase in viscosity, the vitamin C deficiency and the good response to testosterone propionate and adrenal cortical extracts point to disease of the adrenal cortex, while the hypotension, the pigmentation and possibly the flat sugar tolerance curve suggest coincident disorder of the adrenal medulla.[22] Since there is an interrelationship between the adrenals and the other ductless glands, especially the anterior pituitary, the relatively small sella turcica, 15 per cent undersize, may be of some significance.

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20. Kracke and Parker,[9] p. 684.

21. Selye, H.: The Effect of Testosterone on the Kidney, J. Urol. **42**:637 (Oct.) 1939; cited by Garb and Wise,[2a] p. 367.

22. Harrop,[13] p. 308.

There is naturally no way of determining whether the possible derangement of the adrenal glands is a concomitant primary disturbance associated with the syndrome of dyskeratosis congenita with pigmentation, dystrophia unguium and leukoplakia oris, with the resultant sequelae of malnutrition and chronic infection, or whether they are secondarily affected as a sequel of the chronic infection and malnutrition. Sarason [23] proved by autopsy findings that distinct morphologic changes occur in the cortex of the adrenal gland in patients who have suffered from malnutrition, hypertension and inflammatory diseases.

It is interesting to note that Wile,[24] in the discussion of Engman's patient, thought of the possibility of the presence of some malignant change, such as an abdominal neoplasm involving the kidney and suprarenal gland.

SUMMARY

I have summarized the laboratory data and special examinations which were performed and have interpreted the results of the treatments given to 1 of 2 brothers with the syndrome of dyskeratosis congenita with pigmentation, dystrophia unguium and leukoplakia oris for the purpose of ascertaining the possible presence of Addison's disease, which was suggested by the symptoms and physical signs.

There was an increase in the band neutrophils, a rise in sedimentation rate, hypoproteinemia, hypercholesteremia and an increased urinary excretion of creatine. These correspond with the expected findings in the patient who had a chronic infection and was suffering from malnutrition and a wasting disease.

The presence of dysfunction of the adrenal glands (hypoadrenalism) is suggested by symptoms of asthenia; loss of weight; positive results from Rowntree or Schellong tests; cutaneous pigmentation, which is deepest in the areas exposed to light; tests indicating androgen deficiency; vitamin C deficiency; flat sugar tolerance curve; increased viscosity of the blood; relative achlorhydria; increased urinary excretion of creatine; the good response of the leukokeratotic patches to testosterone propionate, which is similar in its beneficial action on the adrenal glands to the hormones of the adrenal cortex; the improvement in the mental and physical condition of the patient, and the partial regression of the leukoplakic patches of the oral mucosa following oral therapy with adrenal cortical extract. This hypoadrenia either may be associated with the syndrome of dyskeratosis congenita with pigmentation, dystrophia unguium

23. Sarason, E. L.: Adrenal Cortex in Systemic Disease, Arch. Int. Med. **71**:708 (May) 1943.

24. Wile, U. J., in discussion on Engman, M.: A Unique Case of Reticular Pigmentation of the Skin with Atrophy, Arch. Dermat. & Syph. **13**:686 (May) 1926.

and leukoplakia oris or represent a secondary effect of the chronic infection and malnutrition.

This contribution presents another chronic disease of the skin with suggestive clinical and laboratory evidence of pathologic alterations in the adrenal glands which has previously been reported in a case of mycosis fungoides with bullous lesions.[2]

219 East Nineteenth Street.

PRIMARY LICHEN AMYLOIDOSIS

Report of Necropsy

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AND
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DEPOSITS of amyloid in the skin associated with widespread systemic deposits have become more generally recognized recently. Primary amyloidosis of the skin must be exceedingly uncommon, however, the first report in the American literature appearing in 1931.[1] This was based on European, not American, cases. For the condition to be considered primary, there should be no evidence of deposits of amyloid in the viscera. This can be ascertained after complete postmortem examination; hence any such diagnosis during life cannot be more than presumptive. The following case fulfils these requirements.

Previous reports of this case have appeared, once in 1939 before the Philadelphia Dermatological Society [2] and prior to that by Herman and Lyon in 1921.[3] The present report summarizes the findings which appeared in these reports and the subsequent course.

REPORT OF A CASE

J. R., a Spaniard residing in Cuba from 1889 to 1906, suffered a severe burn with boiling oil, from which he recovered promptly, and contracted malaria, which lasted for months because of inadequate treatment, during the Spanish American War. Before that, in 1893, it was noted that he had a high erythrocyte count. In 1897 he had what was thought to be an attack of appendicitis and in 1900 an attack of renal colic, which was relieved when he passed several calculi. Another attack of renal colic in 1914 led to the discovery of a renal calculus. He refused operation until a third attack, in 1919, when his right kidney was removed at the Methodist Episcopal Hospital. At that time he was found to have an erythrocyte count of 11,400,000 per cubic millimeter, a leukocyte count of 11,600 per cubic millimeter and a hemoglobin content of 115 to 120 per cent (method not stated). No cyanosis, splenomegaly or other signs of polycythemia vera could be detected. After operation, his erythrocyte count dropped to 5,500,000 per

* From the Ayer Clinical Laboratory of the Pennsylvania Hospital.

1. Winer, L. H.: Local Amyloidosis of the Skin, Arch. Dermat. & Syph. **23**:866 (May) 1931.

2. Greenbaum, S. S.: Lichen Amyloidosus and Prurigo Associated at One Time with Pseudopolycythemia and Visceral Suppuration, Arch. Dermat. & Syph. **39**:380 (Feb.) 1939.

3. Herman, L., and Lyon, B. B. V.: Pseudopolycythemia: Extraordinary Blood Changes in a Patient with Renal Calculus, Ann. Surg. **73**:223 (Feb.) 1921.

cubic millimeter and his hemoglobin content to 108 per cent. Thirteen days after operation his leukocyte count rose to 260,000 per cubic millimeter for some unexplained reason. The differential count was as follows: polymorphonuclear neutrophils, 74 per cent; lymphocytes and monocytes, 17 per cent, and the remainder, basophils and eosinophils. His leukocyte count gradually fell to normal, and the erythrocyte count remained normal. At no time were any abnormalities noted in the shape and size of the erythrocytes. Pathologic examination of the right kidney indicated renal calculus with pyelonephritis and perinephritis.

In 1928, he was seen by one of us (S. S. G.) because of an extensive, extremely pruritic papular eruption distributed over the lower extremities, which he stated had been present since 1918. A provisional diagnosis of lichen planus obtusus was made. Roentgenologic irradiation had no influence on the eruption. He was observed during 1929 and then not again by one of us (S. S. G) until 1938.

In the meantime (1934) he was admitted to the Pennsylvania Hospital because of partial urinary obstruction produced by an enlarged prostate with a large median bar associated with prominent trabeculations and several small sacculations of the bladder. His urine was normal except for a few pus cells. The Wassermann reaction was negative. He stated that he had been well except for an attack of severe precordial pain and syncope which kept him in bed for a week about a decade before. A transurethral resection of 3 Gm. of tissue from the neck of the bladder, consisting of hypertrophied nonmalignant fibromuscular tissue, relieved his urinary obstruction.

When seen in 1938 by one of us (S. S. G.), he had pruritic, acutely developed strophulus-like lesions of the trunk. On the legs, particularly the outer surfaces, were many lesions similar to those seen in 1928. They were hard, discrete, pink, elevated papules from the size of a pinpoint to that of a pinhead after the scales covering them were removed to expose their smooth surfaces. Itching occurred when the parts were touched. Cutaneous scratch tests indicated faint susceptibility to flounder, herring, salmon, shad, lamb, liver, goat's milk, olives, oranges, peas, peaches, pecans and red and green peppers. A positive reaction was elicited to a local Congo red test. Histologic examination of one of the cutaneous lesions revealed amyloid infiltration of the papillary layer and hyperkeratosis. His blood cell count was normal. His urine contained a distinct trace of albumin and many leukocytes of unknown source.

On his final admission to the Pennsylvania Hospital, Oct. 14, 1941, at the age of 72 years, he gave a history of intermittent claudication, dyspnea, edema of the ankles and oliguria of a year's duration. Administration of digitalis gave temporary relief. On physical examination, his temperature was normal, pulse rate 80 to 100 per minute, respiratory rate 20 per minute and blood pressure 210 systolic and 120 diastolic. He was well developed and well nourished, showing some respiratory distress. His heart was enlarged. A systolic murmur was heard at the base of the heart. Occasional extrasystoles were present. Rales were noted at the bases of the lungs. Edema of the legs extended to the thighs. Extensive cutaneous lichenoid eruptions associated with decided hyperpigmentation, especially at the sites of pressure, were noted. Electrocardiographic evidence of severe myocardial damage due to hypertension and coronary disease was obtained. He now had a slight anemia (4,200,000 erythrocytes per cubic millimeter and a hemoglobin content of 84 per cent). His urine contained a few hyaline casts, a trace of albumin and from 12 to 15 leukocytes per low power field. About ten days before death, a tender fusiform mass was felt in the epigastrium. He died instantly while straining at stool on Nov. 17, 1941.

Abstract of Necropsy (performed by Dr. Victor Kiarsis three hours after death).—Externally a small, soft, pedunculated nodule, 8 mm. in diameter, covered by smooth pink skin lay over the sternal region. The skin over the elbows and the knees was covered by several dry, elevated, fine, scaly plaques. Microscopically the growth over the sternum consisted of an encapsulated fibromatous nodule with fibers arranged in whorls. Sections of the skin from the legs exhibited discrete, homogeneous, pale eosinophilic, almost acellular, areas which occurred in the corium just beneath the epidermis. With Mayer's stain, these areas took the reddish violet hue characteristic of amyloid.

An extensive degree of arteriosclerosis involved the aorta and the coronary, splenic and iliac arteries. In the aorta, the intimal covering of many of the yellow atheromatous plaques was replaced by ulcers, on which were attached soft, friable, red-brown masses. The right renal artery was obliterated by a firm fibrous mass (the right kidney having been removed surgically years before). In the abdominal aorta just below it and in the orifice of the left renal artery was a fusiform aneurysm about 11 by 6 cm., which presented several ulcerations of the intima that had dissected the layers along the outer circumference of the aorta as far as the bifurcation and partly down the right iliac artery. The lumen of the right iliac artery was almost completely obliterated by a thrombus, and the lumen of the left iliac artery, greatly narrowed, appeared to communicate with the false lumen of the aorta. Saccular dilatations were present in the left iliac artery. There was no evidence grossly or microscopically that these changes were syphilitic in origin. The arteriosclerotic changes in the coronary vessels associated with calcification had produced sufficient narrowing of the lumens to lead to myocardial scars. The heart was enlarged, indicating some previous existence of hypertension since there were no valvular lesions other than mild sclerosis of age. The pulmonary conus was a trifle prominent. The lungs were emphysematous. The pulmonary vessels were unobstructed.

The spleen and liver were atrophied. The left adrenal was normal and the right partially atrophied. The left kidney, although showing evidence of previous compensatory hypertrophy, was nevertheless scarred by vascular changes. Punctate hemorrhages were scattered along the pelvis and ureter, which ran unobstructed to the bladder. The bladder was small and thick walled, with conspicuous trabeculations. Some ridges and scars lay in the region of the trigone and prostatic part of the urethra. The testes, epididymes, pancreas, thyroid, remnants of thymus, accessible lymph nodes, gastrointestinal tract and thoracic duct were not altered. The bone marrow from the lumbar vertebra was red and soft.

Microscopic studies of all the major organs failed to reveal any deposits of amyloid except in the skin. The lumbar bone marrow contained a few islands of erythropoietic and myeloid cells scattered throughout an abundance of fat.

The chief pathologic findings were extensive arteriosclerosis of the aorta, with a dissecting abdominal aortic aneurysm; arteriosclerosis of the left iliac artery, with small saccular dilatation; arteriosclerosis of the coronary arteries, with myocardial infarction of the posterior part of the right and left ventricular walls; arteriosclerosis generally; thrombosis of the right iliac artery and obliteration of the right renal artery; operative absence of the right kidney; absence of portions of the lateral lobes and the median bar of the prostate (transurethral resection); trabeculation of the bladder; pulmonary emphysema; arteriosclerotic scars of the left kidney; pedunculated fibroma of the skin over the sternum and primary amyloidosis cutis.

COMMENT

Systemic amyloidosis secondary to chronic suppurative infections such as tuberculosis is common. Primary systemic amyloidosis, a form not associated with infections, multiple myeloma or tumors are distinctly uncommon. In 1939, Koletsky and Stecher [4] reviewed the findings in 24 cases and called attention to the occurrence of localized and systemic forms. In the localized variety, the amyloid was limited to one or possibly two organs or there was extensive involvement of one with slight and relatively insignificant deposits in other organs. Although they reported the occurrence of amyloidosis of the skin in 8 of the 24 cases, in none was this the only or the chief site of deposition. Recently Lindsay and Knorp [5] brought the study of primary systemic amyloidosis up to date by compiling the reports since Koletsky and Stecher's review. There are now 39 recorded cases of primary systemic amyloidosis, and in none was the disease confined to the skin.

The formation and deposition of that peculiar substance called amyloid because of its behavior with iodine and sulfuric acid and other stains is unexplained both in the secondary and in the primary form. It is apparent, however, from differences in staining qualities alone that amyloid is not a single substance but a complex variable substance or substances consisting of protein and polysaccharide fractions (Hass and Schulz,[6] Hass [7] and Hass, Huntington and Krumdieck.[8] The pathogenesis of amyloidosis is still unknown, although it has been speculated that antigen-antibody reactions are incurred in its production. Such might conceivably be the case in chronic suppurative infections but would not be directly operative in the primary forms. In our patient, infection of long standing did not exist. The colon bacillus infection of the urinary tract disappeared when the right kidney was removed in 1919. Although it is possible that this infection may have existed for several years prior, it could not have been severe. Whether it had any relation to the papular eruption which was first noticed by the patient about the time of operation is doubtful. Moreover, there is no evidence that

4. Koletsky, S., and Stecher, R. M.: Primary Systemic Amyloidosis: Involvement of Cardiac Valves, Joints and Bones, with Pathologic Fracture of the Femur, Arch. Path. **27**:267 (Feb.) 1939.

5. Lindsay, S., and Knorp, W. F.: Primary Systemic Amyloidosis, Arch. Path. **39**:315 (May) 1945.

6. Hass, G., and Schulz, R. Z.: Amyloid: I. Methods of Isolating Amyloid from Other Tissue Elements, Arch. Path. **30**:240 (July) 1940.

7. Hass, G.: Studies of Amyloid: II. The Isolation of a Polysaccharide from Amyloid-Bearing Tissues, Arch. Path. **34**:92 (July) 1942.

8. Hass, G. M.; Huntington, R., and Krumdieck, N.: Amyloid: III. The Properties of Amyloid Deposits Occurring in Several Species Under Diverse Conditions, Arch. Path. **35**:226 (Feb.) 1943.

amyloid developed in the skin at this time, its presence having been recognized for the first time in 1939, long enough for the cutaneous disease itself to have been responsible for its formation. Since the history and necropsy findings gave no evidence of active chronic infection, one must conclude that the amyloidosis was not secondary to infection. Neither could it have been secondary to a neoplasm, for none was recognized at autopsy.

Amyloidosis secondary to multiple myeloma likewise could be dismissed on the basis of findings in the bone marrow at necropsy.

A further problem which remained unexplained was the polycythemia which existed prior to nephrectomy and then disappeared. No evidence of this disease existed during his several admissions to the Pennsylvania Hospital, and the lumbar bone marrow, normally rather active, was decidedly hypoplastic. It is questionable, too, whether this episode contributed to the formation of amyloid.

In primary systemic amyloidosis, a minimal deposit of amyloid in the liver, spleen, kidneys and adrenals occurs with a maximal deposit in the heart, lungs, skin and mucous membrane.[5] With the routine stains (hematoxylin and eosin) there were no changes in any of these organs to indicate special staining for amyloid. Hence, although it is possible that amyloid existed elsewhere in parts of the body that were not examined, such as the tongue, this seems improbable, because of the lack of symptoms referring to these parts, for example, macroglossia, nasal obstructions and sinusitis. We feel justified, therefore, in considering this a case of primary localized amyloidosis of the skin, cause unknown.

SUMMARY

A case of primary lichen amyloidosis with no evidence of amyloidosis elsewhere on postmortem examination is reported. A discussion of factors associated with primary systemic amyloidosis leaves the pathogenesis of this condition unexplained.

Clinical Notes

HYPERKERATOSIS OF THE PALMS AND SOLES DUE TO THE INGESTION OF QUINACRINE HYDROCHLORIDE

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Recently there have been various types of cutaneous eruptions attributed to the ingestion of quinacrine hydrochloride (atabrine). Many of these eruptions have occurred in members of the armed forces serving in the Pacific, particularly in the New Guinea area. Cases of exfoliated dermatitis, giant urticaria, toxic erythema and certain kinds of lichen-planus-like eruptions have been reported. I believe that this is the first report of a case of hyperkeratosis limited to the palms and soles produced by quinacrine hydrochloride.

REPORT OF A CASE

History.—Major W. K., a 33 year old white man, first came to me for treatment of hyperkeratosis of the palms and soles on Dec. 10, 1945. He had been in the Burma-India Theater of Operations from September 1944 until his return to the United States on Nov. 1, 1945. He stated that he began taking quinacrine hydrochloride in September 1944, 1 tablet a day for the first seven days, 2 tablets a day for the next seven days and 1 tablet a day for the remainder of his stay abroad (fourteen months in all). About three months after use of quinacrine hydrochloride was started his skin became yellow, and in another three months thickened calluses began to develop on the palms. These calluses increased, eventually involving in a patchy fashion most of the palms. Two or three months later (eight or nine months after use of quinacrine hydrochloride was started) a similar hyperkeratosis appeared on both soles. This condition was symmetric and had at times developed fissures.

When the patient consulted me in December 1945, well defined patches of the hyperkeratosis were symmetrically distributed on the palms and soles. No horny plugs were present. The pressure areas were most severely affected, and the central part of the palms and insteps showed some involvement. The skin over the entire body was deep yellow but revealed no change in texture. There was no history of any ingestion of arsenic.

Laboratory Findings.—Repeated scrapings from the hyperkeratotic areas of palms and soles revealed no fungi, and cultures for fungi showed no growth.

Treatment.—Six per cent salicylic acid ointment was prescribed, to be applied night and morning to the hyperkeratotic areas. In addition, five weekly roentgen ray treatments (each 100 r) were given.

Comment.—The aforementioned treatment apparently had no effect on the course of the disease, because it soon became evident that the hyperkeratosis lessened as the yellowish discoloration of the skin subsided. Now that the patient has not taken quinacrine hydrochloride for the past six months, only a slight discoloration and little hyperkeratosis remain.

SUMMARY

The fact that this cutaneous eruption appeared and developed after a long period of intake of quinacrine hydrochloride (atabrine) and improved only as

the effects of quinacrine hydrochloride on other parts of the cutaneous surface lessened would indicate that the ingestion of quinacrine hydrochloride was the cause of the hyperkeratosis of the palms and soles.

120 East Seventy-Fifth Street.

PSEUDOMONAS AERUGINOSA INFECTION OF THE EAR TREATED WITH STREPTOMYCIN

J. LAMAR CALLAWAY, M.D., DURHAM, N. C.

Infectious eczematoid dermatitis of the external ear often presents a difficult problem in therapy. The patient in the following case had a Pseudomonas aeruginosa infection of the external ear which was extremely resistant to treatment until streptomycin was used.

REPORT OF A CASE

O. K. L., a 51 year old professor, was first seen on Aug. 30, 1945 with an acute eczematoid dermatitis of the canal and pinna of the left ear. Culture revealed a pure growth of Ps. aeruginosa. He was given the usual instructions for care of the ear, was told to avoid soap and water and was given 3 per cent salicylic acid in 70 per cent alcohol to apply locally twice daily, with application of a 3 per cent ammoniated mercury ointment at night. In addition he was given 50 r. of superficial roentgen ray therapy. Because he did not improve under this therapy, he was admitted to Duke Hospital on September 9, where he remained for thirteen days. During that time a greenish yellow pus continued to exude from the ear. The severe eczematoid dermatitis of the canal and pinna responded poorly to all local therapy, including compresses, tincture of zephiran chloride locally, 1 per cent aqueous solution of gentian violet medicinal, Castellani's paint and penicillin ointment. In addition he received 1,000,000 units of aqueous solution of sodium penicillin intramuscularly. Throughout his entire stay in the hospital he was under the careful observation of an otolaryngologist. He improved somewhat and was discharged with directions to use 0.5 per cent and later 1 per cent weak solution of acetic acid as an irrigation and as instillation, but this was of little benefit.

Penicillin ointment and penicillin in aluminum hydroxide gel in a strength of 500 units per gram were used, without benefit. An autogenous vaccine, to which he gave a positive reaction after an intradermal test, was administered, without improvement, over a period of several weeks.

On April 19, 1946, eight months after onset, a culture of material from the ear again revealed a pure growth of Ps. aeruginosa, and the ear remained eczematoid and exudative. An aqueous solution of streptomycin, containing 2,500 units per cubic centimeter, was prepared for instillation and as a sponging agent. Within forty-eight hours the oozing and erythema had subsided. The green purulent discharge stopped in two days, and cultures of material taken on May 1 and May 8, were completely negative for Ps. aeruginosa. The ear was again examined by the otolaryngologist and found to be entirely normal.

This experience is reported with the hope that others may find this form of therapy helpful.

From the Division of Dermatology and Syphilology, of the Department of Medicine, Duke University School of Medicine.

DERMATITIS FROM GLASS FABRICS

LOUIS SCHWARTZ, M.D., BETHESDA, MD.

Some months ago an outbreak of dermatitis was reported to the United States Public Health Service as occurring from women's suits and children's coats. Samples of the woolen material and the lining used in the women's suits accompanied the information. Examination of the materials showed that the wool was innocuous but that the lining was made of Fiberglass, which mechanically irritated the skin.[1]

Investigations in New York, where the suits were made, disclosed the fact that also among girls working on the lining dermatitis had developed, and the manufacturer was unaware of the fact that the lining was Fiberglass. The lining was thought to be rayon, which it closely resembled.

It was also learned that another manufacturer using this material as lining for babies' coats had been advised that outbreaks of dermatitis were occurring among babies who wore the coats.

The number of cases of dermatitis reported was so great that both the women's suit manufacturer and the babies' coat manufacturer were compelled to recall all the suits and coats, remove the lining and replace it with other fabric. The manufacturers stated that recalling and relining the garments cost around $30,000. There still remain settlements to be made for damages to the sufferers.

Further investigation revealed that the fabrics had been purchased as surplus property from the government and that the purchaser knew that it was Fiberglass, but the manufacturers of the garments stated that they were not informed of this when they bought the material for linings.

The trade journals and the manufacturers of the Fiberglass fabric were notified of this outbreak of dermatitis, and a warning was given against use of Fiberglass for clothing. It was thought that this would end the matter.

Recently, however, reports have been received of dermatitis occurring from glass fabric being used for binding seams in women's dresses.

This report is made so that physicians will be on the lookout for and maybe able to make the diagnosis in other cases of dermatitis which may occur from irritation caused by Fiberglass in wearing apparel.

From the Office of Dermatology, Industrial Hygiene Division, Bureau of State Services, United States Public Health Service.

1. Schwartz, L., and Botvinick, I.: Skin Hazards in the Manufacture of Glass Wool and Thread, Indust. Med. **12**:142-144 (March) 1943.

TINEA CAPITIS IN SOUTHEASTERN TENNESSEE

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From time to time various authors have reported the incidence of the types of organisms causing tinea capitis in different parts of the world. So far as can be determined there have been no published reports of this nature from this section of the United States. In the face of widespread epidemics of tinea capitis currently noted in other parts of the country it is thought worth while to record the character of the disease in this area.

Between July 1942 and February 1946, 22 consecutive patients with ringworm of the scalp have been seen from whom cultures of infected hairs were made. Three were Negroes and the remaining 19 were white. Their ages ranged from 2 to 9 years; 15 were boys and 7 were girls. The infections were from one week to twelve weeks in duration when first seen.

In 21 cases Microsporum lanosum was cultured, while in 1 Trichophyton crateriforme was isolated. Not a single example of Microsporum audouini was encountered. The vast majority of patients cleared up within a few weeks with local applications of 5 per cent ammoniated mercury ointment. In most instances it was learned that the child had played with a kitten or a puppy shortly before the onset of the scalp lesions. Clinically, many of the affected areas closely resembled the classical picture of infection with M. audouini. Had the appearance of the lesion been the sole criterion for the type of treatment to be used, several would have been needlessly epilated with roentgen rays.

SUMMARY

Twenty-one out of 22 patients with ringworm of the scalp were infected with M. lanosum; the culture for 1 patient showed T. crateriforme. No examples of infection with M. audouini were found, which emphasizes the value of culture studies.

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CORRECTION

In the report of the March 21, 1945 meeting of the Chicago Dermatological Society (ARCH. DERMAT. & SYPH. **54**:744, 1946), the word "correct" in the ninth line from the bottom of page 746, in Dr. Zakon's discussion of the paper by Dr. Frederick R. Schmidt, "Chronic Discoid Lupus Erythematosus," should read "incorrect."

Abstracts from Current Literature

EDITED BY DR. HERBERT RATTNER

TROPICAL ANIDROTIC ASTHENIA (THERMOGENIC ANHIDROSIS) AND ITS RELATIONSHIP TO PRICKLY HEAT. MARION B. SULZBERGER, H. M. ZIMMERMAN and KENDALL EMERSON, JR., J. Invest. Dermat. **7**:153 (Aug.) 1946.

A typical case of tropical anhidrotic asthenia observed on Guam is reported. The clinical and histiologic observations indicated that this disease and ordinary prickly heat are different manifestations of the same fundamental process.

The authors advanced the hypothesis that the sensory disturbances in prickly heat are due to the distention and changes of pressure produced by the secretions of sweat into the plugged ducts and that these symptoms vanish in tropical anhidrosis as the result of the rupture of these ducts allowing free drainage of sweat into the surrounding tissues. Biochemical studies led to observations indicating that the principal systemic manifestations present in this disease are due to hyperventilation as well as to defects in the cooling mechanism of the skin.

An attempt was made to remove the obstructions from the sweat ducts by peeling the skin with ultraviolet light. A return of normal sweating was observed in several portions of the desquamated areas. The patient made a complete recovery in about two months on his return to a temperate climate.

THE TREATMENT OF PYODERMAS WITH AN INTERFACE ACTIVE SOLUTION OF TYROTHRICIN. GEORGE M. MACKEE, MARION B. SULZBERGER, FRANZ HERRMANN and FLORENTINE L. KARP, J. Invest. Dermat. **7**:175 (Aug.) 1946.

The purpose of this investigation was to study the clinical response of a variety of pyodermic diseases to a stable 0.1 per cent solution of tyrothricin in a vehicle capable of penetration into the skin. The solution was applied by inunction and in the form of wet compresses in full strength or in dilutions with one or two parts by volume of boiled tap water.

A favorable clinical response was noted in 232 patients with various cutaneous diseases caused or complicated by pyogenic infection. Included among patients giving favorable response were 112 patients with various types of acne vulgaris.

THE CYTOLOGY OF MOLLUSCUM CONTAGIOSUM WITH SPECIAL REGARD TO THE SIGNIFICANCE OF THE SO-CALLED "VACUOLES." E. MEIROWSKY, S. KEYS and G. BEHR, J. Invest. Dermat. **7**:165 (Aug.) 1946.

The authors present their observations through a series of semischematic drawings to prove that the so-called vacuoles in molluscum contagiosum are not true vacuoles but spherical bodies resulting from the response of the epidermal cell to a virus stimulation.

These bodies appear first within the nucleus and are then extruded into the cytoplasm where they increase in size and number and coalesce to form a large single "H-P" body, containing numerous surface compartments.

SOME NEWER BASES FOR USE IN CUTANEOUS THERAPY. J. G. HOPKINS, J. Invest. Dermat. **7**:171 (Aug.) 1946.

The author presents three types of bases which offer the advantages that the ingredients are all relatively inert and do not react with the constituents of tissue.

The first, an ointment base, consists of a series of polyethylene glycols. They are marketed under the trademark name "Carbowax Compound." By the mixture of Carbowax having molecular weights of 1,500 and 4,000 with propylene

glycol, ointments of any desired consistency can be prepared. This base is an excellent solvent not only for water-soluble substances but also for numerous organic compounds such as sulfonamide compounds, salicylic acid and penicillin. They are convenient for application to the scalp because of the ease with which they can be washed out.

The second base is a bentonite gel and is prepared by mixing 10 to 20 per cent of bentonite with water. The addition of talc facilitates the formation of a smooth gel and the addition of propylene glycol prevents the gel from drying out. Substances such as oils, fats, lecithin or petrolatum emulsify easily in this gel to produce an emulsion having excellent lubricating qualities. This base is suitable for water-soluble drugs such as sodium penicillin, sulfonamide compounds, fatty acids and salicylic acid, as well as the insoluble powders such as sulfur, ammoniated mercury and zinc oxide.

The third, carnauba wax, when mixed with cerasin and liquid petrolatum, makes a base which adheres well to the skin, hardens its surface and repels water. Such cerates are useful as vehicles for active ingredients soluble in oil, such as salicylic acid, chlorophenols or chrysarobin.

IDENTIFICATION OF THE INHIBITORY FACTOR OF RETICULO-ENDOTHELIAL IMMUNE SERUM (REIS) IN A GLOBULIN FRACTION. EDWARD H. FRIEDEN, C. M. POMERAT and LUDWIK ANIGSTEIN, Science **102**:354 (Oct. 5) 1945.

The authors have been able to isolate the albumin and the globulin fractions of reticuloendothelial immune serum by saturating the serum with ammonium sulfate and dialyzing against cold Tyrode's solution until the fluid is sulfate free.

Preliminary experiments demonstrated the following results:

"The albumin fraction obtained from homologous (anti-chick) REIS with a complement fixation titer of 1:1,200 showed no inhibition of outgrowth from fibroblasts or from splenic fragments.

"The globulin fraction, on the other hand, inhibited the outgrowth of fibroblasts and produced clumping of splenic cells to approximately the same degree as controls containing an equal dilution of corresponding REIS.

"Globulin fractions of heterologous (anti-rat) REIS with a complement fixation titer of 1:1,600 did not produce such inhibitory effects on chick tissues in vitro."

Attempts to develop a method of measuring the potency of globulin fractions of the reticuloendothelial immune serum as to both their inhibitory and their possible stimulating action and further fractionation of the globulins are under study.

PATHOLOGIC FINDINGS IN A CASE OF AINHUM: COMPARISON OF THE EPIDERMAL AND VASCULAR LESIONS WITH THE NORMAL TOE. VERNON E. MARTENS and ROBERT F. NORRIS, U. S. Nav. M. Bull. **45**:745 (Oct.) 1945.

Ainhum occurring in a Negro veteran 50 years of age is described, in which the essential lesion appeared to be chronic osteomyelitis. The hyperkeratinization and the hypertrophy of the media of the small arteries previously reported as characteristic of this disease were present in sections taken from 4 grossly normal toes which had been removed from dead white servicemen. The authors suggest that the fibrous constriction of the little toe is not the cause of the destruction of bone but is the result of cicatrization of previously inflamed tissue.

The article includes a review of the literature and several photomicrographs of the pathologic and the normal sections of the toes.

SIMULATING SERUM-SICKNESS REACTION TO PENICILLIN. WILLIAM E. SULLENS JR., U. S. Nav. M. Bull. **45**:752 (Oct.) 1945.

The author reports that penicillin produced an allergic reaction which simulated serum sickness. The symptoms consisted of giant urticarial lesions on the abdomen, the back and the hips, arthralgia of the wrists and the ankles, moderate edema of the feet and the hands, a temperature of 99 F., headache and a moderate general lymphadenopathy occurring six days after a second course of penicillin treatment.

Intradermal tests with a 1 : 10 solution and a 1 : 100 solution of calcium penicillin in isotonic solution of sodium chloride produced no reactions at the sites of injection; however, multiple small areas of urticaria appeared above these areas five hours later. The author was unable to determine whether the reaction was due to penicillin or to an impurity of the product.

TOXIC EFFECTS OF ARSENICAL COMPOUNDS AS ADMINISTERED IN THE UNITED STATES NAVY IN 1944, WITH SPECIAL REFERENCE TO ARSENICAL DERMATITIS. OTTO L. BURTON, GEORGE W. JUSTYN and LAURA T. ANDERSON, U. S. Nav. M. Bull. **45**:783 (Oct.) 1945.

In 1944 medical officers of the Navy administered a total of 396,144 doses of arsenical compounds. A total of 381,475 injections of oxophenarsine hydrochloride were given, resulting in 67 reactions, of which 5 were fatal, giving a ratio of reactions to doses of 1 to 5,694 and a ratio of deaths to doses of 1 to 76,295. A total of 12,398 doses of neoarsphenamine were given, resulting in 13 reactions, of which 3 were fatal, giving a ratio of reactions to doses of 1 to 954 and a ratio of deaths to doses of 1 to 4,133.

Arsenical dermatitis constituted 32 per cent of the total reactions and was of the following types: exfoliative, macular, erythematous, urticarial, papular, maculopapular, morbilliform, pustular and vesicular. Premonitory signs were present in many cases, and this fact suggests the necessity of careful examination and questioning of each patient before an arsenical drug is administered.

ANAPHYLACTOID (SANARELLI-SHWARTZMAN) REACTION FOLLOWING THERAPEUTIC ANTITYPHOID INJECTIONS. JULIAN LOVE and RICHARD H. DRISCOLL, U. S. Nav. M. Bull. **45**:1108 (Dec.) 1945.

A fatal reaction occurred in a young white man following a second intravenous injection of antityphoid vaccine given within a twenty-four hour interval as nonspecific therapy.

At autopsy the finding of petechiae throughout the parenchymal organs and brain and of massive necrosis of the liver and the kidneys indicated a general anaphylactoid reaction. The authors state their belief that the pathologic changes are similar to those obtained by Sanarelli and Shwartzman in experimental animals.

The reaction can be avoided by allowing an interval of at least forty-eight hours between injections.

CASE OF KERATODERMIA BLENNORRHAGICUM (GONORRHEAL DERMATITIS). JOHN R. GATELEY, U. S. Nav. M. Bull. **45**:1159 (Dec.) 1945.

A case of keratosis blennorrhagica is reported, in which the patient was observed and treated aboard a carrier in the Pacific. This patient, a young white man, presented a classic clinical picture characterized by articular pains, headache, fever, slight urethral discharge and symmetric bilateral eruptions of the skin of the hands and the feet, the lesions developing into vesicles and pustules with incrustation and pseudokeratinization. A history of sexual intercourse, leukocytosis (10,500 cells), a temperature of 101 F. and the recovery of gonococci from cutaneous lesions aided in establishing the diagnosis.

The disease was treated by internal administration of sulfathiazole and application of silver nitrate (10 per cent) to the local cutaneous lesions.

SKIN LESIONS OF RHEUMATIC FEVER. ALEX D. CAMPBELL, GEORGE C. GRIFFITH and WILLIAM H. LEAKE, U. S. Nav. M. Bull. **46**:360 (March) 1946.

This discussion of the cutaneous manifestations of rheumatic fever is based on observations made by the Rheumatic Fever Unit stationed at the United States Naval Hospital, Corona, Calif.

Erythema annulare rheumaticum of the Lehndorff and Leiner type was the most common lesion encountered. Certain other erythematous eruptions, subcutaneous

nodules and purpura were also found to be specific for rheumatic fever. Erythema nodosum and erythema multiforme were found to be nonspecific.

Erythema annulare rheumaticum was not invariably associated with valvular heart disease and did not have prognostic significance.

It was the authors' impression that more urticaria was present in their patients with rheumatic fever than ordinarily found in their other hospitalized groups.

RODIN, South Bend, Ind.

HERPES ZOSTER AND CHICKEN-POX. JAMES TAYLOR, Brit. M. J. **2**:385 (Sept. 22) 1945.

Dr. Taylor points out the fully established connection between herpes zoster and chickenpox. He contends that there is sufficient evidence to justify making herpes zoster a notifiable disease.

THE INITIAL TREATMENT OF TROPICAL ULCER. F. E. STOCK, Brit. M. J. **2**:388 (Sept. 22) 1945.

An effective treatment for tropical ulcer is described by Stock. On three successive days the ulcer is painted with a saturated solution of potassium permanganate, which is allowed to dry. Undermined skin at the edge of the ulcer is trimmed off with scissors and painted with the same solution. The whole surface is then dusted lightly with pure iodoform and covered with cotton. At the end of three days any of the familiar treatments with antiseptics, ointments, occlusive dressings or skin grafts can be employed.

HAEMOLYTIC DISEASE AND CONGENITAL SYPHILIS IN SIBLINGS. MARJORY N. MCFARLANE, Brit. M. J. **2**:494 (Oct. 13) 1945.

The author reports on a family which provides information on the supposition that congenital syphilis may cause erythroblastosis. The blood of the mother, aged 34, was group A_1 and Rh negative (rr). Her husband was overseas. In 1935 the patient gave birth to a premature living baby girl whose blood was of group A_1 and Rh positive. In 1939 she was delivered of a full term baby boy who died of icterus gravis neonatorum (hemolytic disease, type II). In 1941 she had a miscarriage at six months. The fourth pregnancy resulted in a full term living baby girl whose blood was of group O and Rh negative.

In the second child erythroblastosis was present, but evidence of syphilis was lacking. The presence of powerful anti-Rh agglutinins may reasonably be supposed to have been responsible for the fetal hemolytic disease and possibly for the subsequent miscarriage. The outcome of the fourth pregnancy, however, indicates that evidence of syphilis may be present in the mother and infant without fetal erythroblastosis, even in a family in which hemolytic disease has previously appeared. Hemolytic disease did not develop in this child in spite of strong anti-Rh agglutinins in the mother's blood, owing to the lack of the Rh-positive antigen in the fetal cells.

There is at present no satisfactory evidence to show that congenital syphilis or other infection can bring about by itself the clinical and pathologic features of fetal erythroblastosis, and blood group incompatibility is the only proved cause of this neonatal disorder.

REHABILITATION OF PATIENTS SUFFERING FROM SKIN DISEASE. R. MASON BOLAM, Brit. M. J. **2**:539 (Oct. 20) 1945.

In 1943, seventy beds were allocated for the rehabilitation of patients in dermatologic cases among military personnel. During two years 800 men have been admitted; 584 of these have been returned to duty and 216 have been discharged from the service.

Patients with many types of cutaneous disease apart from those of a chronic, widespread, intractable nature will benefit from rehabilitation, and much can be

done by showing the patient how to live with his disease and how to apply his treatment correctly.

The psychiatric aspects of these patients deserve detailed study since a considerable number are poorly adjusted, displaying anxiety to a varying degree, whereas others have a pronounced self-centered disposition. During the period of convalescence the utmost tact and sympathy are necessary in handling special cases in which it must be decided whether a man may resume his former occupation or should engage in work along new lines. Facilities provided include woodwork, leatherwork or needlework, entertainment, a library, educational courses, lectures and the opportunity to work on the grounds and the farms in the neighborhood.

Types of cutaneous diseases which benefit from rehabilitation of the patients are: (1) dermatitis seborrheica, (2) eczema, (3) impetigo, (4) pyodermatitis, (5) furunculosis, (6) dermatitis due to a sulfonamide compound and (7) lichen planus.

In treating dermatitis seborrheica of the trunk and the extremities, the authors have found the following prescription far superior to the more popular sulfur-salicylic acid ointment:

Solution of coal tar N. F...
Prepared calamine N. F....
Zinc oxide.....
Peanut oil.....
} 1 drachm (3.88 Gm. or Cc.) of each

Petrolatum to make 1 ounce (30 cc.)

An interesting observation is the fact that men recovering from dermatitis due to a sulfonamide compound are unable to wear khaki clothing, necessitating testing of the skin with uniform material before they are returned to the service. The author recommends that rehabilitation of patients with cutaneous disease should be introduced for the civil population.

SHAW, Chattanooga, Tenn.

PATHOGENESIS OF ENCEPHALITIS DUE TO SALVARSAN. STEPHAN VON PASTINSZKY, Dermatologica **87**:12 (Jan.) 1943.

Two young men, one with primary and secondary syphilis and the other with a syphilitic chancre, were treated with a bismuth compound and mild doses of neoarsphenamine (0.3 to 0.45 Gm. every four days). After four intravenous injections in the one case and three in the other severe encephalitis developed, which in 1 instance was associated with dermatitis due to arsphenamine. The patients recovered. The serum of the 2 patients elicited positive Prausnitz-Küstner reactions in test persons and passive anaphylaxis against arsphenamine in rabbits. The results of the tests, the accompanying dermatitis and the onset after small doses are considered as evidence that the encephalitis is due to hypersensitivity to neoarsphenamine.

EXPERIMENTAL STUDIES ON THE QUESTION OF THE CAUSE OF PEMPHIGUS. HULUSI BEHÇET, BERTA OTTENSTEIN, GÜZIN TOKSOY and SATI ESER, Dermatologica **87**:113 (March) 1943.

The authors tried to duplicate Lindenberg's experiments on animals, which seemed to prove the viral nature of pemphigus. They inoculated 19 rabbits with blood serum, blister contents and brain emulsion from 4 patients with pemphigus and 1 with epidermolysis bullosa hereditaria. These test materials were introduced by intratesticular, epidermal, intracutaneous and subcutaneous routes. During an observation period of two months no animal showed any pemphigus-like lesions of the skin.

HISTOLOGIC FINDINGS AND HERZBERG'S STAIN FOR VIRUS IN PEMPHIGUS. PERIHAN CAMBEL, Dermatologica **87**:127 (March) 1943.

Three male patients who died of pemphigus showed at autopsy microscopic hemorrhages of the brain, increased pigmentation of ganglions, fatty degeneration

of the liver and lack of cells of the splenic pulp. These signs are regarded as infectious-toxic; others—for instance, bronchopneumonia—are regarded as secondary complications. Two patients showed fibrosis of the testes, 1 of whom had in addition chronic thyroiditis of the Riedel type. Herzberg's stain did not reveal any virus.

ERYTHROPLASIA OF THE GLANS PENIS (BOWEN'S DISEASE OF THE MUCOUS MEMBRANES). L. M. PAUTRIER, Dermatologica **87**:169 (April-May) 1943.

Pautrier has always maintained that erythroplasia of Queyrat and Bowen's disease of the mucous membranes are identical.

He reports on a 57 year old man with oozing tender bright red lesions of the glans penis and some slightly infiltrated papillomatous lesions of the corona glandis. In this case the erythroplasia started with lesions similar to those seen in balanitis circinata erosiva. Two or three small lymph nodes were palpable in the inguinal area. The histologic examination revealed changes characteristic of Bowen's disease.

The author regards this condition and others of the same sort not as precancerous but as truly epitheliomatous, requiring surgical intervention.

A NEW TYPE OF GRANULOMATOSIS WITH GENERALIZED TUMORS SIMULATING MYCOSIS FUNGOIDES WITH FATAL OUTCOME. L. M. PAUTRIER, Dermatologica **87**:190 (April-May) 1943.

A 37 year old man had almost generalized soft, red-brown, partly ulcerating tumors which looked clinically like mycosis fungoides. The histologic examination, however, revealed a different picture. The tumors consisted of lymphocytes and cells which were hard to classify but which looked like young histiocytes. The patient also had obstructing tumor masses inside the nose and an ulcer of the epiglottis. He suffered from bilateral tuberculosis of the pulmonary apexes. The blood picture ruled out leukemia. Aleukemic leukemia did not seem probable.

This, in the author's opinion, is another case of the group entitled "nonclassifiable granulomatosis," a term which he introduced in 1937.

A PECULIAR FORM OF SKIN ATROPHY. W. LUTZ and H. PICARD, Dermatologica **88**:79 (Aug.) 1943.

Since the autumn of 1941 a 17 year old girl has shown on her extremities livid noninfiltrated discolorations which are either circumscribed and of round or oval shape or confluent and forming a bizarre bandlike pattern. She does not recall any exposure to intense cold. The lesions feel doughy; the overlying skin gradually becomes as thin as cigaret paper. Before the terminal stage of atrophy is reached, one finds edema and widening of the papillary layer of the corium, widening of the increased blood vessels and marked dilatation of the lymph spaces but no inflammatory infiltration. The livedo-racemosa-like design speaks against primary macular atrophy and acrodermatitis atrophicans chronica; the distribution, however, suggests a functional disturbance of the blood vessels as the underlying etiologic factor.

MELANOTIC NEVUS OF THE CHEEK; APPARENTLY UNDERGOING MALIGNANT DEGENERATION, DUE TO A LARGE UNDERLYING FOREIGN BODY GRANULOMA WHICH HAS DEVELOPED AROUND BONE FORMATION. L. M. PAUTRIER, Dermatologica **88**:110 (Aug.) 1943.

A 44 year old woman had had since infancy three pigmented nevi of the right cheek. During eight weeks the largest of the lesions became tender, elevated and infiltrated. A diagnosis of nevus-epithelioma was made. All nevi were removed with the electric cutting current. The changes observed histologically were those of a nevus, without signs of malignant changes, and of an enormous foreign body granuloma which had developed in the deep part of the corium and subcutis around

some osseous formation. A rudimentary sebaceous cyst might have caused the metatypic bony growth. The author feels that the constant irritation underneath the nevus would sooner or later have caused malignant degeneration of the nevus.

LEUKODERMA ACQUISITUM CENTRIFUGUM (SUTTON) AND THE REPRODUCTION OF THE PRESENTATION OF SIMILAR CUTANEOUS CHANGES ON A PANEL OF THE ALTAR OF ISENHEIM. H. KUSKE, Dermatologica **88**:282 (Nov.-Dec.) 1943.

The author reports 4 new cases of leukoderma acquisitum centrifugum. In the course of his studies of this disease he observed on a panel of the altar of Isenheim, which depicts the temptation of St. Anthony, a demon showing cutaneous changes characteristic of leukoderma acquisitum centrifugum. (This is not the man covered with tumors, which are manifestations either of leprosy or of syphilis.) It is, of course, doubtful whether Grünewald had ever seen a human model exhibiting numerous pigmented spots surrounded by depigmented areas.

ATYPICAL CHONDRODYSTROPHIA OF THE TYPE MORGUINO ASSOCIATED WITH FOLLICULAR ATROPHODERMA. G. MIESCHER, Dermatologica **89**:38 (Jan.-Feb.) 1944.

A 6 year old girl showed at birth beginning kyphoscoliosis and other signs of chondrodystrophia fetalis calcarea. This disturbance is accompanied with a tendency of the skin toward follicular atrophy. There are many areas of pseudopelade on the scalp. Changes of the skin of the trunk and the extremities resemble atrophoderma vermiculatum of the face. In this case, however, the face is not involved.

EXTENSIVE PAGET'S DISEASE WITHOUT FORMATION OF CANCER DURING CONSTANT OBSERVATION FOR FOURTEEN YEARS. G. MIESCHER, Dermatologica **89**:45 (Jan.-Feb.) 1944.

The cutaneous disease of a 42 year old woman started with a pinhead-sized red fissure of the right nipple fourteen years previously, after the birth of a child. Two years later, on histologic examination the diagnosis was Paget's disease of the epidermis and the milk ducts. At the time of the author's last observation the whole right breast and the adjacent parts of the trunk were covered with oozing, eroded and crusted confluent lesions. A movable soft small gland could be felt in the right axilla. A second histologic examination, in 1943, showed the same classic polymorphous Paget's cells as did the first biopsy. The disease at the time of the author's last observation involved also the orifices of the sebaceous glands. Fractional doses of roentgen rays and subsequently grenz rays for recurrences at the periphery brought about complete epithelization of the eroded area.

BOWEN'S DISEASE (WITH RARE LOCALIZATION BETWEEN THE SECOND AND THE THIRD LEFT TOE). P. ROBERT, Dermatologica **89**:55 (Jan.-Feb.) 1944.

For three years a 47 year old man noticed in the second interdigital space of his left foot itching rhagades, which were unsuccessfully treated as intertriginous and mycotic eczema. The verrucous, thickened, sharply circumscribed lesion showed histologically the typical epidermal changes of Bowen's disease.

URTICARIA PIGMENTOSA OF PECULIAR, LIVEDO-RACEMOSA-LIKE DESIGN. W. STALDER, Dermatologica **89**:72 (Jan.-Feb.) 1944.

Two years ago a 19 year old woman noticed on the inner surface of the thighs reticular confluent hyperemic and edematous streaks, which later flattened. They assumed a brownish-blackish color. Exposure to cold and rubbing caused edematous swelling. Needle pricks were followed by local highly red urticarial elevations which spread to neighboring streaks. Areas farther away also became elevated. The histologic examination showed numerous chromatophores and small perivascular infiltrations of lymphocytes and scanty mast cells in the papillary

layer. In the corium there also were occasionally some perivascular mast cells. A diagnosis of cutis marmorata pigmentosa was ruled out. The scant presence of mast cells, even their absence, does not speak against urticaria pigmentosa in the opinion of the author and other dermatologists whom he mentions.

A Case of Trichofolliculoma. G. Miescher, Dermatologica **89**:193 (April-May) 1944.

For a year a 46 year old woman with a few pigmented nevi and small angiomas on her face had noticed on her right cheek a small nodular elevation, from the center of which a tuft of hair emerged. Whenever she pulled out some hairs, some serum exuded from the same opening. After extirpation of the tumor the histologic examination revealed an enormous follicular orifice with about eighty lanugo hairs. There were many secondary follicular pockets present; all hairs, though, left the skin through the same orifice. Sweat glands and signs of inflammation were missing.

A New Type of Familial and Hereditary Agenesis and Dystrophy of the Hair. Alice Ullmo, Dermatologica **90**:75 (Aug.-Sept.) 1944.

The father and the grandfather of a boy and his sister, described in detail, seemed to have shown identical malformations. Eyebrows, eyelashes and axillary and pubic hair were missing. The son had no beard. The scalp showed tonsure-like alopecia of the central parts, while the rest of the hair of the scalp was black and thick. There were small keratotic follicular plugs disseminated over the entire body. The teeth and the nails, however, were not deformed. The girl suffered from psychosis, and the boy was mentally retarded.

Confluent Eruption of Verrucae Planae of the Hands, the Forearms and the Neck, Simulating Epidermodysplasia Verruciformis, Associated, However, with Verrucae Vulgares. L. M. Pautrier, Dermatologica **90**: 86 (Aug.-Sept.) 1944.

For five or six years a 33 year old man has suffered from verrucae planae spreading over the dorsal surfaces of his hands, his forearms, his face and his neck. There are large verrucae vulgares on the dorsa of the fingers and over the metacarpophalangeal joints.

The abundance of the small lesions which, by the way, surpass the size of ordinary verrucae planae suggests epidermodysplasia verruciformis; the coexistence of vulgar warts and the histologic structure of the smaller lesions, however, only permit a diagnosis of verrucae planae. Only few cells show vacuolation of malpighian cells. The author raises the question whether there are perhaps not fundamental but quantitative differences between epidermodysplasia verruciformis and verrucae planae.

Cause of Phagedenic Soft Chancre. N. Melczer, Dermatologica **90**:157 (Oct.) 1944.

In order to solve the question why a soft chancre occasionally becomes phagedenic, pus from a phagedenic chancroid was inoculated into the skin of the same patient or into that of healthy persons. Invariably, phagedenic ulcerations were produced. In smears of pus or scrapings from phagedenic chancroids, streptobacilli, other bacteria and the elementary bodies of a filtrable virus were seen. If filtrates containing the pure virus alone or pus alone were inoculated into animals, negative results were obtained. Filtrates containing the virus were rubbed into scarified skin of healthy persons or intracutaneously injected. No ulcers resulted. If, however, mixtures of the filtrate with various strains of bacteria were inoculated, or if the filtrate was implanted in pyodermic lesions, phagedenic ulcerating lesions developed. These phagedenic pyodermic lesions could be transmitted to other test persons

Helen O. Curth, New York.

Society Transactions

NEW YORK DERMATOLOGICAL SOCIETY

Hans J. Schwartz, M.D., *President*

George C. Andrews, M.D., *Secretary*

May 22, 1945

A Case for Diagnosis (Ichthyosis Hystrix? Psoriasis?). Presented by Dr. A. Benson Cannon.

R. O., a 9 month old white Italian boy, was born at full term with normal delivery and was apparently healthy except for an eruption which occupied the same sites and distribution as at present. The lesions have become more scaly and of a darker red color. The diet has consisted of evaporated and goat's milk reenforced with vitamin D, without any apparent change in the disease. The mother thinks that orange juice aggravates the eruption. There are no subjective symptoms.

Examination shows a healthy-looking, well developed child with numerous red, linear, macular lesions in wavelike formation, covered with gray scales in layers. The eruption is most pronounced on the sides of the body, the back and the sides of the face. Long, wide bands, 6 to 8 inches (15 to 20 cm.) in length by several inches in diameter, are noticeable along the lines of the ribs. Numerous red, scaly plaques resembling psoriasis are noticed in the scalp, with apparently normal skin between the plaques. There were no changes in the nails.

Scrapings from the lesions were negative for fungus.

DISCUSSION

Dr. John C. Graham: The linear character of the lesions plus the fact that they have been present since birth would, in my opinion, make ichthyosis hystrix the diagnosis of choice.

Dr. Eugene F. Traub: The distribution on the trunk, where whirls can be seen, is certainly a congenital anomaly, but the eruption is not sufficiently cleancut for ichthyosis hystrix, and in a patient of this age one has to wait until further development before coming to a final conclusion.

Dr. Maurice J. Costello: I think that the eruption is nevoid in character. I saw a case similar to this, in which the eruption was much more extensive, consisting of streaks of telangiectasis.

Dr. Fred Wise: I have the impression that the lesion is a nevus.

Dr. Howard Fox: There is no doubt about this being a generalized, linear nevus. The question of psoriasis being present since birth is unusual. I have never heard of a case like that.

A Case for Diagnosis (Linear Nevus? Lichen Planus Atrophicus?). Presented by Dr. Maurice J. Costello.

L. D., a 6 year old girl, was first seen by me on May 3, 1945, when she showed a generalized scratched, papular, urticarial eruption. Examination at that time showed another eruption, entirely different in type, involving the left lower extremity, which her mother stated had been present about three years and was zosteriform in distribution, extending from the midthigh to the calf, and more prominent on the lateral aspect. The individual lesions varied from the size of a matchhead to that of a half dime and were sharply marginated. Some of the lesions

were red and others hyperpigmented, with depressed centers. Examination with a magnifying glass showed the center of the lesions to be atrophic and studded with tiny follicular plugs. Many of the lesions were discrete, but some were coalesced to form bizarre patterns.

DISCUSSION

DR. FRED WISE: The lesion appears to me to be a linear nevus. Histologic changes often simulate the appearance of chronic lichen planus in eruptions of this character, and the scarring is produced by involution of the lesion.

DR. A. BENSON CANNON: I favor the diagnosis of lichen planus. She has lichenoid, shiny papules on the margin of the involved areas which look strikingly like lichen planus.

DR. LESLIE M. SMITH (by invitation): I rather think that it is atrophic lichen planus.

Nevus Pigmentosus. Presented by DR. PAUL E. BECHET.

J. O., a woman aged 47, stated that she had a single papillomatous pigmented nevus between two toes of her left foot, which had been present since birth. There has been a rapid increase in size in the past five years. She was sure that it had doubled in size. There were no subjective symptoms.

The lesion has a mulberry-like appearance with considerable pigmentation. It is somewhat pedunculated and measures approximately 15 mm. in length by 9 mm. in width. The patient is presented for discussion as to whether the lesion should be removed or left in situ.

The patient also has an ordinary contact dermatitis on her face and neck, which is irrelevant to the presentation.

DISCUSSION

DR. MAURICE J. COSTELLO: I think that this is a simple pigmented nevus and can easily be removed without risk to the patient.

DR. LESLIE M. SMITH (by invitation): I should destroy the lesion by electrocoagulation.

DR. JOHN C. GRAHAM: I agree that it is benign and perfectly safe to remove.

DR. HOWARD FOX: This is a soft pigmented nevus, with a pedicle showing its benign nature. It could be removed even without anesthesia, following which the base could be thoroughly cauterized.

DR. FRANK C. COMBES: I wonder what the pigment is.

DR. PAUL E. BECHET: I am deeply grateful for the discussion and shall remove the lesion. My reason for the presentation was to ascertain the opinion of the society as to the advisability of intervention. Many years ago, a patient with a lesion in the same location was presented before the Manhattan Dermatologic Society by the late Dr. Oulmann. The majority of dermatologists present at the meeting advised against its removal. Some years later Dr. Oulmann reported to the society that the patient had had the lesion excised by some one else and had died within the year from multiple metastases. The relation of this tragic occurrence impressed me with the necessity of extreme caution in deciding whether or not to remove the type of growth presented by the patient under discussion.

Generalized, Progressive Scleroderma Associated with Changes in the Lungs, the Larynx and the Esophagus. Presented by DR. HOWARD FOX.

M. G., aged 47, a salesman, was first seen by me on July 9, 1937. Six months previously, following an attack of influenza, he began to have general malaise and first noticed changes in the skin. These changes were limited to the hands and the upper part of the chest and clavicular region. The hands and fingers were swollen and the overlying skin moderately hidebound. There was no tapering of the fingers and no history or signs of Raynaud's disease. The fingers had a peculiar yellowish

color. The upper part of the chest and clavicular region were somewhat shiny and striated, the upper portion presenting short, parallel, white ridges, varying from ⅛ to 1 inch (0.3 to 2.5 cm.) in length. The lower part of the area showed patchy pigmentation and some depigmentation. The skin in these areas was definitely hidebound. The finger nails showed longitudinal ridges and furrows and a tendency to be convex anteroposteriorly as well as laterally.

A general physical examination, made just previously at the Mount Sinai Hospital (Consultation Service), showed no abnormalities except scleroderma and some unidentified roentgenologic changes in the lungs.

The patient's chief complaints were a dry, hacking cough and dyspnea on exertion. He was advised to do no work and to live in a warm climate. For the past eight years he has spent much of his time in Florida or southern California. His cutaneous lesions do not bother him and have not increased in extent or severity in the past eight years. The hoarseness of voice, dry cough and dyspnea on exertion have gradually become worse.

For the past few years he has been under the care of Dr. James Alexander Miller, who wrote in December 1941: "I have about finished my study of Mr. M. G. Investigation of his respiratory function was made at the Presbyterian Hospital by Dr. Richards. He reported the unusual finding that with perfectly adequate ventilation the patient showed striking oxygen deficiency on moderate exercise and also was unable to absorb inhaled oxygen to relieve such deficiency. Dr. Richards says that this would be perfectly consistent with the diagnosis of pulmonary fibrosis involving the alveoli rather than the peribronchial tissue, and that is just what I think this man has." In a recent letter (May 17, 1945) Dr. Miller added that "in addition to a bilateral pulmonary fibrosis, he also has a dilated esophagus and a certain amount of cardiospasm. A bronchoscopic examination shows a thickening of the mucous membrane of the larynx and trachea, characteristic of scleroderma." Also, Dr. A. Wilbur Duryee took an electrocardiogram and encephalogram in May 1943, which "showed a disturbance of the cortex such as is found in 80 per cent of the cases of scleroderma."

DISCUSSION

Dr. Fred Wise: The coincidence of pulmonary fibrosis in association with progressive scleroderma has been emphasized in several recent publications.

Dr. Maurice J. Costello: I saw this man some years ago, when I was associated with Dr. Howard Fox, and at this time, in addition to beginning difficulty in breathing, he also had difficulty in swallowing, which he now claims has cleared up. I think that his dyspnea is due to true pulmonary fibrosis in addition to restriction of respiratory movement caused by infiltration of the muscles of the skin.

Dr. George M. Lewis: A patient recently studied at the New York Hospital showed the site of the sclerosing process to be in muscles predominantly rather than in the skin.

Dr. Howard Fox: The involvement of the respiratory tract is extremely unusual. I have seen many cases of progressive scleroderma, and I have never seen a case like this and do not know whether such has ever been presented before the society. This man has pulmonary as well as laryngeal and esophageal involvement. There was no cancer, as one physician at the Misericordia Hospital thought. He has been treated with an enormous amount of vitamins of all kinds, and lately he has been taking oxygen, which seems to help him. That is the only treatment he is receiving.

A Case for Diagnosis (Lupus Erythematosus? Pemphigus?). Presented by Dr. Frank C. Combes.

M. G., a man aged 60, was referred to me with the diagnosis of pemphigus; it impressed me rather as being lupus erythematosus, with lesions of the lips and oral mucosa predominating. The patient's health has always been good except that diabetes was discovered four months ago, his fasting blood sugar content being

230 mg. per hundred cubic centimeters at that time. In July 1944 he noticed a bluish white line on his lower lip. Some time later scaly patches developed on his forehead. Two months later an erosion appeared on the left side of his lower lip, which responded to treatment with radium. Two similar lesions were destroyed by electrodesiccation.

At present there are three nummular, erythematous patches on his forehead, partially covered with a dry, adherent scale. In some areas the surface is glazed and atrophic, the scale tending to be attached at the borders. On the buccal mucous membrane on the right side is an erythematous patch. On the lips are several crusted erosions. The vermilion borders of the lips are poorly defined, and in some places there are bluish white areas of hyperkeratosis and hemorrhagic crusts.

DISCUSSION

DR. MAURICE J. COSTELLO: If I had one diagnosis to make I should say lichen planus. The lesions on the buccal mucosal membrane and border of the lip suggest this disease.

DR. A. BENSON CANNON: I think that it is a most unusual case and that the diagnosis would rest between lupus erythematosus and lichen planus. I feel much as Dr. Costello does, that if I had to choose between the two I should probably choose the latter. The patient has an extensive involvement of the mucous membranes, the vermilion border of the lips and the lower part of the entire mucous membranes of both cheeks, more especially the right; he has linear and circinate white lesions that look much as though he had them painted with silver nitrate, and he even has lesions of the hard palate. The red area on the right side of the forehead could well be lichen planus. I think that the final diagnosis rests on histologic study, one section from the forehead and one from the mucous membranes of the mouth.

DR. HOWARD FOX: Often when a diagnosis seems to lie between lupus erythematosus and lichen planus, after the case has been sufficiently studied, it is apt to be proved to be lupus erythematosus. Between these two I should favor lupus erythematosus.

DR. FRED WISE: I strongly favor the diagnosis of pemphigus, which at present appears to be in a mild form but may at any time flare up into severe pemphigus vulgaris, with fatal results. A fair proportion of the Senear-Usher eruptions terminate in pemphigus vulgaris, ending in death.

DR. ANTHONY C. CIPOLLARO: This is a confusing clinical picture, and I doubt that one biopsy specimen will tell the story. I think that the patient should be thoroughly studied, and several biopsy specimens from various areas will be required before a diagnosis can be made.

DR. FRANK C. COMBES: I saw this patient this morning for the first time. He was sent in with a probable diagnosis of pemphigus, and naturally my efforts were all toward disproving that diagnosis. The symptoms seem to me to point to lupus erythematosus. I cannot see lichen planus as the diagnosis, but if I had to choose between lichen planus and pemphigus I should choose the former.

Mycosis Fungoides. Presented by DR. FRANK C. COMBES.

In H. W., a man aged 61, there have for the past six years developed irregularly shaped, bizarre, erythematous patches on various parts of his body, which have remained more or less fixed and have been accompanied with no subjective symptoms other than occasional, inconsequential pruritus. On the right elbow are cicatrices designating the site of two bean-sized nodules removed for histologic examination. One nodule on the right wrist was irradiated. All erythematous patches have faded somewhat after irradiation therapy. At present the lesions are situated on his arms, thighs and buttocks and average 15 cm. in diameter. They are flat, the borders are festooned, the erythema is of varying intensity, in places

they are telangiectatic and they do not disappear entirely on pressure. In some sites there are areas of skin of normal color, roughly circinate, varying in size up to 2 cm. In a few areas there is a suggestion of deep nodule formation and scaling. The eruption is roughly symmetric.

Examinations of the blood have given constantly normal results. Histologic examination of the nodules and erythematous patches have suggested nothing but a benign granuloma and chronic inflammatory tissue respectively, although clinically it had been my impression that mycosis fungoides was the correct diagnosis. One of the nodules recently removed from his elbow showed the typical polymorphic infiltration characteristic of this dermatosis. The Wassermann reaction of the blood was negative.

DISCUSSION

DR. MAURICE J. COSTELLO: I think that this patient has mycosis fungoides.

DR. ANTHONY C. CIPOLLARO: I agree with the diagnosis.

DR. HOWARD FOX: I agree with the diagnosis.

DR. FRED WISE: On clinical grounds, I favor the diagnosis of mycosis fungoides.

DR. LESLIE M. SMITH (by invitation): I believe that this is mycosis fungoides or some other member of the lymphoblastoma group.

DR. FRANK C. COMBES: I am glad that the majority of opinion is in favor of mycosis fungoides. This man's condition has grown progressively worse, although individual lesions have responded temporarily. I hesitated to make a definite diagnosis because the changes were so uniform and the cellular infiltration so uniform, both suggesting a condition much more benign in nature than mycosis fungoides. However, as time goes on, I believe that there will be changes typical of this disease. The erythematous lesions show some slight improvement; the lesion on his wrist, which was a nodule about 2 cm. in diameter, received 150 r and resolved in two weeks.

Postarsphenamine Vitiligo. Presented by DR. A. BENSON CANNON.

H. O., a white housewife aged 47 years, was admitted to Vanderbilt Clinic on Dec. 27, 1943, suffering with generalized postarsphenamine dermatitis of three weeks' duration. She married at the age of 21, lived with her husband three months and had one miscarriage. The husband was found to be syphilitic. The patient had no treatment until seven months ago, since which time she has had two injections of neoarsphenamine and one injection of a bismuth preparation each week until the outbreak of the present eruption. Her skin has been red and crusted, oozing, burning and itching, accompanied with much swelling of the face and lower extremities. She has felt extremely weak and has had nausea.

General examination showed a well developed and nourished woman in considerable distress. The skin was universally red, scaling and crusted. The feet, legs and areas around the orbits were considerably swollen.

Laboratory tests showed a high blood arsenic content, of 0.15 mg. per hundred grams of dry specimen. Several subsequent tests were also high for arsenic. The urine was essentially normal, as was the blood cell count, except for a slight leukocytosis. The Wassermann and Kline reactions of the blood were negative, and the spinal fluid was normal. The complete chemistry of the blood was essentially normal.

Treatment consisted of daily injections of sodium thiosulfate and later of calcium thiosulfate; 250 mg. of vitamin C was given daily, and 4 cc. of crude liver was given intramuscularly twice a week for about three months. The patient gradually improved, both in physical well-being and in the appearance of the skin. Eventually the skin was entirely free from dermatitis. As the eruption cleared, white spots were noted all over the body and extremities, with an apparent increase of pigment surrounding the white areas. The patient's skin is dotted all over with pea-sized to silver dollar–sized white macular spots.

DISCUSSION

There was no discussion of this case. All agreed with the diagnosis.

Exudative Discoid and Lichenoid Chronic Dermatosis. Presented by Dr. Fred Wise.

J. W., a boy aged 15, was seen at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on July 6, 1944, presenting lesions of nine months' duration. The father is Jewish and the mother Gentile. There is no allergic history in the family or in the patient. He had the first attack two weeks after moving into a new apartment. Intradermal tests of all the common allergens were said to give negative results. He complains of severe itching. Because of this and the disfigurement caused by the appearance of the lesions, mental symptoms developed and he threatened to commit suicide.

He was hospitalized at the Kings County Hospital, where he received eight injections of typhoid vaccine. He improved while there but had a relapse soon after his discharge from the hospital. He was also treated with nine injections of Hapamine (a chemical combination of histamine and despeciated horse serum globulin), without benefit.

The patient presents a generalized, dusky, erythematous, oozing, eczematized eruption on the trunk and extremities. The lesions are elevated and consist of matchhead–sized to split pea–sized macules, discrete and coalesced, forming ill defined circular and oval plaques and bizarre-shaped patches. Many of the lesions are excoriated and covered with crusting and scaling. They are more pronounced on the cubital and popliteal areas, where they are arranged in a circular fashion. As in all eruptions of this kind, the skin of the penis is involved.

The patient was ordered to receive the following treatments: baths in a solution of potassium permanganate; phenobarbital, 25 mg., and thiamine hydrochloride, 5 mg., each three times a day, and testosterone propionate, 25 mg., by intramuscular injection three times weekly.

DISCUSSION

Dr. Howard Fox: Some call this disease discoid eczema. I think that this case falls into the class that Rosen first described and later was studied by Sulzberger and Garbe.

Dr. A. Benson Cannon: I agree with Dr. Fox and the presenter that this is a classic example. This is the youngest patient I have ever seen, and I have been observing such cases since 1916. I think that this is a contact dermatitis and that he can get absolute cure by a change of environment.

Dr. Leslie M. Smith (by invitation): Most of you are probably familiar with the fact that about a year ago the El Paso Chamber of Commerce mailed to a good many of the dermatologists in the East copies of their weekly bulletin, advising that patients with disseminated neurodermatitis be sent to the Southwest to be treated by sunshine. We of the El Paso medical profession do not approve of this type of publicity and do not feel that our climate is the answer to the problem of neurodermatitis, and we have requested that the Chamber of Commerce discontinue this publicity. I have seen the majority of the cases of neurodermatitis and chronic discoid lichenoid dermatosis which the publicity man had in mind. Many of the patients have improved, some after a few weeks, but more of them after a prolonged rest, while some have received no benefit or have gotten worse. I feel sure that the change of environment and the rest from nervous strain at home have more to do with the benefit than the dry air and sun. I believe, however, that, particularly in the cases of exudative conditions, there is a benefit from the dry air and cautious sun bathing in some of the cases.

Dr. Maurice J. Costello: I agree with the diagnosis.

Dr. Frank C. Combes: I agree with the diagnosis. The problem in these cases is the origin of the lymphadenopathy. This patient also has enlargement of all his superficial lymph nodes. This adenitis in many cases is a simple irritative

phenomenon. I have followed several patients and found the histologic picture to change to giant follicular lymphadenopathy and later polymorphous cell sarcoma, with a fatal outcome. Favorable response of the dermatosis to treatment will check this metamorphosis. Best results have followed a change of environment. Other medical therapy has given unsuccessful results, except temporary improvement following radiotherapy to the nodes.

DR. FRED WISE: This is the youngest patient afflicted with this dermatosis that I have encountered. The eruption appears to occur almost exclusively in male Jewish patients.

Lupoid Sycosis. Presented by DR. FRED WISE.

G. F., a man aged 24, registered at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on May 22, 1945, presenting lesions of one year's duration. He gives no history of previous disorders of the skin.

A small pustule first appeared on the right cheek. A month later many more pustules developed in the same area in a circular manner. The rest of the bearded region then became affected. He was treated in the Army with penicillin salve and with injections of penicillin every three hours continuously for fifteen days, for a total of one hundred and twenty injections, without any apparent improvement. A silver dollar–sized area on the right cheek was then exposed to roentgen rays for "ten minutes," the rest of the face being shielded with lead. This was not followed by any inflammatory reaction. Most of the hair in the irradiated area has not regrown since. He was then sent to Walter Reed Hospital, where he was treated with ammoniated mercury salve, alcohol and boric acid soaks and with other salves, without result. The patient stated that the bald spot on the right side of the cheek has the same appearance as before the roentgen ray exposure except for the lack of growth of hair.

On the right cheek, along the mandible and extending below to the neck is a fairly well defined patch, 7 by 4 cm. in diameter, which is erythematous, almost entirely denuded of hair growth, atrophic and revealing fine folds. The entire bearded region, including the front and sides of the neck and the upper lips, is also affected with numerous follicular pustules pierced by hairs and covered with crusting and scaling.

The routine laboratory tests gave normal results.

DISCUSSION

DR. HOWARD FOX: I am surprised that penicillin has not done him any good. I have seen a number of articles that speak highly of the use of penicillin in sycosis.

DR. EUGENE F. TRAUB: Before the diagnosis of lupoid sycosis is finally accepted, the question of the single ten minute dose of radiation has to be considered, because this may possibly be a case of loss of hair follicles. In regard to penicillin therapy, I had an experience with a case of sycosis recently, of eleven years' standing, in addition to folliculitis, involving the hair of the forearms of five years' duration. This patient was given penicillin locally. He seemed to be much irritated after this particular variety of penicillin was applied, and I thought that he was possibly sensitive to the vehicle, so I incorporated the next batch in Aquaphor. He kept getting progressively worse during the period in which penicillin was applied to the skin. He was then treated by injection in the usual manner, and after the first one or two injections he swelled up to twice his size and became so violently ill that treatment had to be discontinued. In this case of sycosis vulgaris the penicillin seemed to be actually an irritant.

DR. JOHN C. GRAHAM: I have had the same experience as Dr. Traub with penicillin in sycosis. I have a patient who was irritated by penicillin ointment. However, he is now using tyrothricin in liquid form and is tolerating it well.

DR. A. BENSON CANNON: I hope to show 2 patients in parallel cases of general sycosis, 1 treated with sulfathiazole locally and the other with penicillin injection,

and both patients were cured. One is going about now without a lesion. This is the most beautiful cure I have ever seen from use of two different drugs, and I could not tell the difference in the beneficial effect between the two.

DR. GEORGE M. LEWIS: I have recently seen two eczematous reactions to the local application of penicillin.

DR. MAURICE J. COSTELLO: In my experience the local application of penicillin has been gratifying. It would be most unusual if there were not some people who were not sensitive to a new medicament. A specialist in pulmonary disease told me that in patients given insufflations of penicillin and oxygen there occasionally developed dermatitis venenata of the perioral regions and generalized urticaria and angioneurotic edema later. In the patients found to be sensitive to penicillin, I should like to suggest the application of Quinolor Compound Ointment (10 per cent benzoyl peroxide and 0.5 per cent Quinolor [a mixture of 3 chlorine derivatives of 8-hydroxyquinoline] in a base of equal parts of petrolatum and wool fat).

DR. PAUL E. BECHET: The condition struck me as an ordinary sycosis and the atrophy and superficial scarring on both cheeks a possible radiodermatitis. If I understand the history correctly, the patient told Dr. Wise that he had received a ten minute exposure to roentgen rays. I should like to testify that I have also had excellent results with Quinolor, but I have also seen it fail in a few cases. On the whole, however, it has, in my experience, proved of great value in the treatment of this obstinate dermatosis.

DR. FRANK C. COMBES: I do not think that we should talk so glibly of the effect of penicillin locally in pustular dermatoses. In sycosis vulgaris there are many factors which must be considered, including the type of organism, the susceptibility of the person, his type of skin and associated disease. The question also arises, why has this patient lupoid sycosis rather than sycosis vulgaris? Is it a peculiarity of the infectious agent or the person? Probably the former is Staphylococcus albus. It has been my practice when giving penicillin to follow it either with penicillin by mouth or with toxoid injections. In spite of this, relapses are common in sycosis.

DR. FRED WISE: The patient never suffered from a reaction produced by the topical use of penicillin. There is no evidence of alopecia or dermatitis caused by roentgen ray treatment. The atrophic area and alopecia are manifestations of lupoid sycosis.

A Case for Diagnosis (Mycosis Fungoides? Arsenical Dermatitis?). Presented by DR. GERALD MACHACEK.

S. M., a Negro woman aged 35, shows an eruption of four years' duration, which began on the sides of the trunk as pigmented spots that did not itch. At that time she was taking Ex-lax and Feen-a-mint. She received some intravenous injections from a local physician, following which she began to itch all over. So far as she knows, the Wassermann reaction of the blood was negative before these injections were started and has always been negative.

On entering Vanderbilt Clinic on Jan. 6, 1944, she showed a symmetric generalized eruption involving the trunk and extremities but not the hands, feet, face or scalp. The lesions are deeply pigmented, elevated patches, palm sized and smaller. Some are gyrate or configurate in shape. Many plaques are infiltrated, and some are scaly. A biopsy specimen showed psoriasiform dermatitis with a possibility of premycotic mycosis fungoides. Dried blood showed 0.22 mg. of arsenic per hundred grams. The Wassermann and Kline reactions of the blood were negative. Examination of the blood showed a hemoglobin content of 11.9 Gm. (82 per cent); 4,350,000 red blood cells; 5,300 white blood cells; polymorphonuclear leukocytes 68 per cent; leukocytes 29 per cent, and eosinophils 3 per cent. The serum cholesterol level was 174 mg. per hundred cubic centimeters. Cephalin flocculation was normal.

The patient was treated with injections of calcium and sodium thiosulfate, without any beneficial effects. Fractional doses of roentgen rays were slightly beneficial. Dental roentgenograms and examination showed nothing abnormal.

Laboratory examination gave these results: plasma vitamin C, 1.3 mg. per hundred cubic centimeters; serum phosphatase level, 2.2 mg.; inorganic phosphatase level, 3.4 mg., and urea nitrogen content, 12 mg.; there was a faint trace of bilirubin. The serum protein content was 6.1 mg., albumin content 4.2 mg., globulin level 1.9 mg. and urea nitrogen content 7 mg. per hundred cubic centimeters. The erythrocyte sedimentation rate was 35 mm. in one hour. A roentgenogram of the chest was normal. The patient received intravenous injections of typhoid vaccine, with no appreciable change in condition. While in the hospital she had an attack of blepharoconjunctivitis, with fever, and perirectal abscess.

A second biopsy, done on Aug. 29, 1944, showed lymphoblastoma (mycosis fungoides). A third biopsy specimen of the papular lesions on the chin showed "tuberculosis cutis."

NOTE.—This case was previously presented at the New York Academy of Medicine, Section of Dermatology and Syphilis, in February 1945, by Dr. Gerald Machacek.

DISCUSSION

DR. MAURICE J. COSTELLO: I agree with the diagnosis.

DR. PAUL E. BECHET: On the back, in the scapular areas, the lesions are circinate.

DR. ANTHONY C. CIPOLLARO: I cannot offer any diagnosis, but I certainly do not think that this is a clearcut case of either mycosis fungoides or arsenical dermatitis. The diagnosis depends on the histologic changes. Further studies and observation will no doubt reveal the true nature of this disease.

DR. HOWARD FOX: I agree that the condition in this case is a difficult one to diagnose, but I am surprised that no one has made the attempt to find fungus microscopically or by culture. I suggest that such examinations be made.

Contact Dermatitis of the Hands. Presented by DR. FRANK C. COMBES.

S. S., a dentist aged 51, has had a dermatitis of both hands for over two years. It has varied in severity, at times involving only a few areas on the backs of his fingers. For four months following its inception it was confined to the second finger on the right hand. At the present time it involves all the fingers, and there is some scaling of the palms. Scrapings have been persistently negative for fungi. There is no evidence of a fungous infection or of any focal bacterial infection in his teeth, tonsils or sinuses. He has a reaction (2 plus) to a trichophytin test but gives a history of tinea capitis at the age of 8. Patch tests with 2 per cent procaine hydrochloride on two occasions have elicited negative reactions.

DISCUSSION

DR. ANTHONY C. CIPOLLARO: I do not believe that this is contact dermatitis. I think that this man has an eczematous eruption belonging to the group of localized, atopic dermatitis or nummular eczema. I have had similar cases, and all efforts to ascertain the cause have been fruitless. It is significant that this patient has lesions even when away from his work, a fact which favors the diagnosis of localized atopic dermatitis.

DR. A. BENSON CANNON: I agree with the presenter that this is contact dermatitis, probably occupational, and the solution of the problem depends on the detective work with sensitization tests of the skin.

DR. EUGENE F. TRAUB: More consideration should be given to the question of fungous infection as a factor in this case. He might have nail involvement; he has a positive trichophytin reaction, which is a point in favor of fungous infection. He has lesions of a vesicular character, which are not common except in rare cases

of atopic eczema or dermatitis of the hands. This may explain why the eruption does not entirely disappear when he is on a vacation. There is no doubt that he has a dermatitis superimposed on this, and my feeling is that most dentists are difficult to treat and keep on one form of treatment consistently. I believe that they will try to use various medicaments, and this, too, may be a factor in the chronicity of this case.

DR. GEORGE M. LEWIS: I believe that there is probably a contact causation in this case. I agree with Dr. Traub that it is extremely difficult to keep dentists on a strict regimen as regards exclusion of possible sensitizers.

DR. MAURICE J. COSTELLO: If this patient were not a dentist, I wonder whether the question of contact dermatitis would come up at all. I agree with Dr. Cipollaro.

DR. FRANK C. COMBES: I agree that persons do not just contract contact dermatitis. It depends on three factors, namely, cellular susceptibility and exogenous and endogenous factors. Undoubtedly in this instance, some constitutional factor is present. It may be a good idea to have him see an allergist. There is no doubt that he is suffering from a neurosis, and I agree with Dr. Lewis and Dr. Traub that he has just enough knowledge of medicine to make him meddle with himself. Even tonight he stated that when he covers his lesions with collodion he feels better; also when he puts them into extremely hot water it relieves the itching.

CLEVELAND DERMATOLOGICAL SOCIETY

B. Levine, M.D., *President*

G. W. Binkley, M.D., *Secretary*

May 24, 1945

Erythema Chronicum Migrans. Presented by DR. H. N. COLE and DR. J. R. DRIVER.

W. S., a white woman aged 56, was born in the United States. Three years ago a red ring developed on the anterior surface of the neck. Later two similar lesions appeared. All three have gradually enlarged and become confluent. She has used iodine locally. Recently a new lesion has appeared just below the confluent lesions.

On the front of the neck is a thin, raised, firm, red, serpiginous lesion in a roughly circular outline, representing the coalition of several lesions. The lesion is slightly indurated and slightly raised above the surface. Below it there is a nickel-sized annular area, flat in the center. There is no scaling and no vesicle formation. The hemogram and urinalysis gave normal results. A roentgenogram of the chest showed calcified foci. The maxillary sinuses showed thickening of the mucous membranes. There was arthritis in the sacroiliac joints and of the spine.

The biopsy specimen was unsatisfactory. At one end was epidermis of five to eight cell thickness with a slight cellular infiltrate around the vessels in the corium. The endothelial cell lining of the vessels was swollen. The other portion of the section showed the epidermis to be much lower, and the underlying tissue shows swollen, collagenous fibers. There was no evidence of giant cell formation. Collagen tissue was not fragmented.

DISCUSSION

DR. H. N. COLE: There seems to be a slight amount of atrophy in the center of the area, and I am sorry that we did not take a specimen from it also for examination, to see what it would show. I think that one would have to consider the possibility of sarcoidosis, though I never have seen a sarcoid with such a fine line as this patient shows. Usually, when there is an annular type of sarcoid,

there is more atrophy than we find in this patient. As far as she knew, she had never been bitten by a tick.

The patient did have tuberculosis, which apparently is healed.

One would consider granuloma annulare and a gyrate type of chronic erythema, but the line is too fine for the latter.

In 1909 Afzelius reported a case similar to this before the Stockholm Dermatological Society, and in 1911 Balban (Balban, W.: *Arch. f. Dermat. u. Syph.* **105**: 423-430, 1911) reported before the Vienna Dermatological Society an erythema annulare, with epithelial cell, typical of what is found in this case. All Balban's 3 patients had been bitten by wood ticks. That was also true of the patient in Afzelius' case (Afzelius, A.: *Acta dermat.-venereol.* **2**:120-125, 1921).

Lipschutz in 1913 reported cases (Lipschutz, B.: *Arch. f. Dermat. u. Syph.* **118**:349-356, 1913); the disease is usually spoken of after him, "erythema migrans of Lipschutz." However, it was not reported originally by him. Lipschutz considered that this is a rare disease, and it is in this country, though apparently in Sweden there are cases occasionally. It is, of course, a well forested country. Perhaps that has something to do with it, as Afzelius pointed out. The narrow line that is found is fine, slightly raised and of a pinkish color. There is a little evidence of atrophy in the center. It usually starts with a single spot and then spreads. This peripheral type of spread in the case Lipschutz reported reached a diameter of 50 cm., an extensive process on one thigh, so they do get to be of large size and they may last for several years. In 1 patient of Balban's, it lasted for a year.

It is difficult to conceive how this process could follow the bite of a wood tick. It has been compared, also, with swine erysipelas, but in that disease there is not the picture seen here. Moreover, there are chronic manifestations which these patients never have.

Parapsoriasis. Presented by Dr. H. N. Cole, Dr. J. R. Driver and (by invitation) Dr. A. R. Minadeo.

F. W., a white girl aged 18, is employed as a photographer. There is no history of any similar disease in the family. The patient stated that she perspires little except on the face, even in hot weather. She has always been well. She has been troubled since she was 4 years old, and perhaps earlier, with an eruption, which is persistent but worse in the summertime. There is no pruritus in connection with it.

There is a generalized eruption made up of plaques that are not particularly well defined, covered with red, silvery scales. In some places, scaling is more prominent than in others, e. g., over the thighs the scaling is much more extensive and almost confluent. The face is exempt. On some areas there is no scaling, but there is a retiform type of brownish pigmentation with a certain amount of atrophy. This is particularly noticeable in the inner aspect of the upper part of the arms and the inner aspect of the thighs. The hair, lips, teeth and nails seem to be normal. There is no evidence of involvement of the mucous membranes.

A histologic report of skin from the back by F. D. Weidman, University of Pennsylvania, is as follows:

In specimen A the stratum corneum was not clearly defined as such, because its cells merged insensibly with those below. For the most part, they were barely recognizable. The granular layer was not thick. The epidermis, as a whole, was moderately thickened. The interpapillary pegs extended to uniform depths, and, although they merged from place to place and broadened, they still maintained a regularity of character. The prickle cells were of young type, as indicated by their richly chromatinized nuclei. Basal cells were active and frequently underwent metaplasia into prickle forms. Some of the prickle cells toward the surface showed intracellular edema, and the same was true along the basement membrane.

In the corium there were no pronounced pathologic changes, excepting in the center of the lesion. A narrow zone of inflammatory change could be traced

immediately below the epidermis throughout the entire section. It consisted of hyperplastic capillaries and lymphocytes, with a few polymorphonuclear leukocytes. The nuclei of the few fibroblasts present were pyknotic. Sweat glands were not exhibited, and elastic tissue was absent except for a few delicate strands under the epidermis.

Specimen B was from the medial surface of the arm. The picture in this specimen was entirely different from that in the preceding specimen. The epidermis was atrophic and did not exhibit tendencies to parakeratosis. Immediately below the epidermis appeared a fairly broad zone of loosely fibrillar tissue containing numerous small capillaries, a few chromatophores and scattered fibroblasts and lymphocytes. The picture was that of young scar formation or residual fibrosis.

The eruption has been resistant to external treatment, including much superficial roentgen irradiation.

Parapsoriasis en Plaque. Presented by DR. H. N. COLE, DR. J. R. DRIVER, and (by invitation) DR. A. R. MINADEO.

R. S., a white woman aged 21, is an office worker. She has not had any previous cutaneous disease, and there was no history of a similar disease in the family. In the winter of 1943 an eruption developed on the arms, and this later spread to the legs and trunk. There is little pruritus with it. The patient has always had much dandruff. She occasionally takes Ex-lax. She is a well developed and nourished person.

There was extensive pityriasis of the scalp at the time of examination on Dec. 29, 1944. There is an eruption that is made up of lesions that are sharply defined and have a tendency in places to assume an arciform shape. They are superficial and present on the arms, trunk, thighs and neck. In some places they are confluent. If anything, the lesions are more extensive on the extensor surface than on the flexor surface. There is some enlargement of the lymph nodes. A salicylic acid lotion was prescribed for the scalp and a tar and ammoniated mercury ointment for the skin.

DISCUSSION OF THE TWO PRECEDING CASES

DR. E. W. NETHERTON: In the case F. W., I thought that some of the lesions on the arms were suggestive of parapsoriasis. However, the other lesions were more inflammatory than is usual in the plaque type of parapsoriasis. The scaling of the lesions on the arms and the legs was superficial and, in many respects, was similar to that of parapsoriasis.

In case R. S., I thought of a fixed drug eruption. Some of the lesions had a variation in color. The lesions in the groin were almost purple, and the lesions on the lateral trunk were oval and had a play of color from a deep violet at the periphery. There was pigmentation on the back that looked like that of a fixed drug eruption.

DR. H. HECHT: In regard to R. S., I think that it is a drug eruption due to phenolphthalein.

In case F. W., if the parapsoriasis started at the age of 4, it would be rare. Although I suppose that it is possible, I do not think that it is parapsoriasis. If one had examined this patient without knowing the history, one would say it is an allergic eruption. The patient stated that she had many dermal diagnostic tests without results. I still think that it must be an allergic eruption that started at the age of 4.

DR. H. N. COLE: I believe that these patients have been receiving ultraviolet irradiation over a period. This has changed the appearance since December 1944. In both those cases, I believe that chronic resistant macular and maculopapular scaly erythroderma would have to be ruled out. Certainly, the girl who has had the eruption since she was 4 years old has not been taking phenolphthalein all those years. I do not know any other entity which would fit in so well here as parapsoriasis.

R. S. has some itching now, but it has been present only since she has been getting irradiation with the quartz lamp.

DR. A. R. MINADEO (by invitation): Dr. Cole misunderstood me in regard to the ultraviolet irradiation. R. S. has had about ten treatments with an Alpine lamp, with some improvement. F. W. had no treatment, with the exception of rose water ointment U. S. P.

DR. BENJAMINE KLINE: Do you regard the condition in R. S. as parapsoriasis as well as that in F. W.?

DR. H. N. COLE: I do.

Urticaria Pigmentosa (Nodular Type). Presented by DR. H. N. COLE, DR. J. R. DRIVER and (by invitation) DR. A. R. MINADEO.

K. B. is a white girl aged 9 months. The parents are living and well. Nobody else in the family has had a similar disease. When the patient was 6 months old, the mother noted a spot on the side of the baby. New lesions have continued to develop, and all have persisted. The baby does not seem to be scratching. She eats a large amount of carrots.

Scattered over the neck, trunk and shoulders are ovoid, raised, nodular, yellowish brown lesions. Many of them are smooth, others have an irregular surface. The palms have a yellowish brown color, and the cheeks have a slight yellowish tinge.

The histologic section showed a low epidermis. Changes of pathologic character were limited to the upper dermis. The lower dermis was normal. There was a diffuse stroma in which there were many cells with a deeply staining nucleus and a large light pink surrounding cytoplasm. There was no evidence of inflammatory reaction. With polychrome methylene blue stain, typical mast cells were seen. There were many open spaces between the cells. There was no giant cell formation. Fat stains were negative for xanthoma cells.

DISCUSSION

DR. A. R. MINADEO (by invitation): I saw this girl about three weeks ago for the first time. There was fine vesiculation on a few of these nodules. The mother stated that this had occurred on previous occasions.

DR. D. R. PRINTZ: I read the articles by Graham Little (*Brit. J. Dermat.* **17**:355, 1905; **20**:232, 1908) and also the American literature on this subject. Dr. Little described a nodular type of urticaria pigmentosa. This case duplicates his entirely. After the lesions are stroked, a fine erythema appears, especially at the base.

At one time it was thought that the pigment in urticaria pigmentosa was due to the mast cells. In this case, although the cells were high up in the dermis, there was even more infiltration around hair follicles and the sweat glands, which is characteristic of urticaria pigmentosa.

DR. J. E. RAUSCHKOLB: I was struck with the color of the baby, which probably modified the lesions of urticaria pigmentosa somewhat. The baby has been ingesting large amounts of carrots and her skin has a Chinese yellow color. Many of the nodular lesions are yellow, and I think that the disorder is carotenosis of the skin.

A Case for Diagnosis (Epidermodysplasia Verruciformis?) Chronic Myeloid Leukemia. Presented by DR. G. W. BINKLEY.

D. M. H., a white woman aged 44, consulted me in May 1940 for an eruption on the hands, which had appeared two years earlier. There were no antecedents who had this condition.

The primary lesion is a small, flat, angular, red-brown papule. There are many of these on the dorsa of the wrists and fingers and the extensors of the forearms. The papules may be single but usually are found in small groups. In these groups

there is a tendency to confluence. There are a few ring forms and parts of rings. A chronic myeloid leukemia was discovered three years ago.

The urinalysis showed normal findings. A Kline exclusion test of the serum gave a negative reaction. Many hemograms were made.

Results of Hemograms

	Erythrocytes	Hemoglobin, Gm.	Leukocytes	Neutrophils, %	Eosinophils, %
11/13/42	4,220,000	11	47,000	65	4
3/22/45	.....	12.5	12,200	61	5
	Basophils, %	Lymphocytes	Monocytes	Myelocytes	Myeloblasts
11/13/42	7	8	2	13	1
3/22/45	4	23	7	0	0

A histologic examination of a typical papule showed a thick layer of loosely attached hyperkeratosis. A papule was made up of a well defined area of acanthosis and an infiltrate in the underlying corium. In the involved area the stratum granulosum was thicker than normal. The cells of the upper rete showed liquefaction of the cytoplasm. The nuclei of these cells were larger than normal. Such changes were severe near the stratum granulosum and less severe in the middle portion of the rete. However, there was some spongiosis of the basal cell layer. Blood vessels in the corium were dilated and surrounded by a cuff of lymphocytes.

Use of yellow mercurous iodide, 0.01 Gm. three times daily for twenty days, was the first treatment. In June 1940 cautery removal of all visible lesions was performed, with prompt recurrence. In 1942, six or seven fractional doses of superficial roentgen irradiation were administered to the upper extremities at the Cleveland Clinic. There was no change. Finally all lesions were refrigerated with liquid nitrogen. The eruption has slowly progressed.

Deep roentgen irradiation was given to the front and back of the chest and abdomen for leukemia.

DISCUSSION

DR. H. J. PARKHURST: I could not differentiate the individual lesions clinically from juvenile flat wart, as their mold and order of appearance were similar, and I will have to be persuaded that was not what they were.

DR. H. N. COLE: The fact that the lesions were present only on one hand to any extent would be more in favor of flat warts.

DR. H. G. MISKJIAN: I had the same impression, and I was taking the presenter's diagnosis lightly. However, after seeing the histologic picture and finding it was so characteristic, I now think that it is epidermodysplasia.

DR. E. W. NETHERTON: I saw this patient in 1942, diagnosed flat warts and treated the disorder as such, without success. The myeloid leukemia is probably unrelated to the cutaneous lesions. However, one must keep in mind the possibility that it might have something to do with the changes around the vessels.

Although I am not well informed on the histology of this disease, I know that clear cells are one of the outstanding features of epidermodysplasia. These same cells are seen in flat warts. I think that the changes in the epidermis are minimum.

Another factor against the diagnosis is that epidermodysplasia verruciformis usually appears earlier in life. As Dr. Cole pointed out, the lesions are more symmetric and more extensive, and some of the lesions are usually more like keratoses. All these are uniformly a flat and angular, pink, skin-colored type of lesion. I think that there were some with linear distribution, all features of juvenile warts.

DR. G. W. BINKLEY: After five years of observation, I began to doubt the diagnosis of verrucae planae. One of the reasons is the color of the papules.

The papules are reddish brown or a dull red color, much redder than common verrucae planae. Verrucae planae may be yellowish brown, but these are highly colored by a persistent vasodilatation, which could be completely removed by pressure.

The patient was aged 38 when lesions appeared. The lesions are bilateral in distribution on the upper extremities.

The biopsy specimen showed a dyskeratosis which simulated flat wart in appearance but also was consistent with epidermodysplasia.

I considered the entity of Hopf which he described under the title "Acrokeratosis Verruciformis" (Hopf, G.: *Dermat. Ztschr.* **60**:227, 1931).

The changes in acrokeratosis are similar from an anatomic viewpoint but differ clinically in that there are lesions on the palms. The patient presented had no palmar involvement.

DR. H. J. PARKHURST: May I remark that in many cases flat warts fail to disappear after treatment?

Cutaneous Horn. Presented by DR. J. H. BARR.

M. C. is a white woman aged 64. She had always been in good health. Systemic review is noncontributory. In June 1944, she noticed that her comb caught in hair behind her left ear. Further observation revealed a small tumor. She applied home remedies, with no effect. The tumor continued to enlarge gradually during the ensuing months, and in the past month there has been a rapid growth. She is well developed and well nourished.

There is a large, well defined tumor mass behind the left ear, having the appearance of a horn. The base measures approximately 9 by 10 cm. It is soft, red and vascular. The remainder of the tumor mass tapers to a point approximately 8 cm. above the base and is characterized by keratinization.

There was no significant lymphadenopathy. The Kline reaction of the serum was negative. The hemogram and urinalysis gave normal results. A roentgenogram of the skull showed no destruction of the bone.

Biopsy of the tumor mass revealed a squamous cell papilloma with much keratinization, showing local invasion of scalp. There was insufficient cellular pleomorphism to warrant a diagnosis of malignant change.

The lesion was widely excised, tissues of the scalp being removed down to the galea. Thiersch grafts were then taken from the left thigh and applied to the aforementioned area. The area is now completely epithelized and shows no evidence of recurrence.

DISCUSSION

DR. J. R. DRIVER: Had I seen this patient, I do not believe that I should have recommended operation. I do not think that there is any cutaneous horn that would assume this size without malignant degeneration at the base. I should have advised use of interstitial radium needles.

Excision, which was performed here, and Thiersch grafts have apparently been successful. It is rather surprising to me, because with a squamous cell lesion one would expect a recurrence in the grafts. One would hesitate to do skin grafting on the base of an epithelioma before being certain that there was not going to be any recurrence. If the tissue which was removed has been preserved, it is possible that review might reveal something.

DR. H. G. MISKJIAN: I did not find a single section that appeared malignant. I think that the conception that the bases of all these cutaneous horns are malignant must be changed. I have seen others that were not malignant.

Fig. 1.—Cutaneous horn on woman aged 64.

Fig. 2.—Horn after removal. The base measured approximately 9 by 10 cm., and the remainder of the mass tapered to a point about 8 cm. above the base.

DR. J. H. BARR: The section was made through the base of the horn. There are about fifteen slides, and they all show the same nonmalignant papilloma.

Acne Conglobata. Presented by A. R. SWEENEY, United States Marine Hospital No. 6 (by invitation).

T. E. H., a white man aged 48, was a marine engineer. His father died at 73 of "heart trouble." The patient's last service was in the South Pacific from September 1944 to February 1945. He has had seventeen surgical procedures, mostly incision and drainage and attempts at resection of sinus tracts about the anal and crural regions.

Following a burn of the face and chest in 1923, pustular lesions appeared in the burned areas. They spread to involve the back, axillas, buttocks and scrotum. Since October 1944, during his service in the tropics, the lesions have been severer and more frequent.

There are multiple keloids on the face, neck and scalp. The skin of the face, neck, trunk and especially the perianal regions, buttocks and crural regions is involved in a scarring process with multiple purulent sinus tracts and hypertrophied tissue. There is an indurated mass about the size of a large orange in the right buttock, surrounded by fibrous tissue and evaginated old surgical scars.

Repeated cultures of material from sinuses showed a growth of Staphylococcus albus. Urinalysis gave normal results. The Kline reaction of the serum was negative, and the basal metabolic rate was 0 per cent.

The biopsy specimen showed a pronounced verrucous hyperplasia of the epidermis with parakeratotic hyperkeratosis, acanthosis and dyskeratosis. A few epithelial pearls with keratinization were in areas of acanthosis. The changes were consistent with pseudoepitheliomatous hyperplasia.

He has received numerous types of treatment, including local medication, autogenous vaccine, ultraviolet irradiation, repeated incision and drainage, filtered roentgen irradiation and 1,000,000 units of penicillin intramuscularly, with no improvement.

DISCUSSION

DR. H. J. PARKHURST: The localization of multiple lesions in the axillas and perianal regions suggests that there may have been an infection of the apocrine glands which would suggest hidradenitis suppurativa, possibly, in addition to the acne conglobata.

DR. H. N. COLE: This patient brings up the point that has been made by Dr. Duemling and others, that men with a tendency to a severe acne—and the same would also apply to those with hidradenitis—are probably not going to do well if they reside in a hot climate. When they return to this country and into a cooler climate, they seem to do better. This man, who was an engineer on a ship, was sent to one of the hottest places in the world, the south coast of Persia. The process immediately began to get bad and has been disabling since.

A Case for Diagnosis (Lichen Sclerosus et Atrophicus?). Presented by DR. E. W. NETHERTON and DR. W. R. HUBLER.

Mrs. F. S., a white woman aged 29, came under observation for the first time on Feb. 16, 1945. The eruption which she presented at that time was limited mostly to the extremities, the lesions being more numerous on the thighs. She stated that for the past year oval and annular, reddish brown lesions had appeared gradually in the aforementioned areas. There were no subjective symptoms. In February the eruption consisted of papules and plaques. The papules were round and angular, flat, varied from the size of a matchhead to that of a split pea, smooth and brownish pink. The larger lesions tended to be oval, with central scaling of a furfuraceous type, and in some of the lesions there was a suggestion of atrophy of the central portion. Some of the lesions were composed of a group of the small papules. On diascopic examination, the lesions could not be completely obliterated.

During the period of observation, which extended from February to the present, the lesions have enlarged slightly and have become smooth and of a white, ivory color. The eruption now consists of small, oval, slightly irregular, raised, white plaques and papules, some of which have a slight amount of scaling and central scarring and possibly atrophy. There are no follicular plugs.

Sections of the biopsy specimen which was taken when she was first seen showed the following changes: the surface epithelium showed a slight amount of hyperkeratosis, there was atrophy of the epidermis with absence of most of the interpapillary pegs, there was lymphocytic infiltration in the papillary and subpapillary layers and there was a slight amount of liquefaction degeneration of the basal layer of the epidermis. The infiltration also involved the pilosebaceous follicles; the middle portion of the corium appeared to be normal.

DISCUSSION

DR. C. L. CUMMER: I do not think that the type of lesion corresponds to the atrophy which has followed the involution in the cases I have had. It looks to me more like a depigmentation than it does lichen atrophicus.

I saw a bluish cast to the skin in my patients as the lesions cleared, especially in 1.

DR. E. W. NETHERTON: The disorder in this case has been a diagnostic problem. When these lesions appeared, they were pinkish brown. Some of them today suggested it, but they were not typical. Early in the course of the disease they developed a furfuraceous shine, with a grayish color. When it was scraped slight scaling could be demonstrated. That went on, finally, to a point at which the lesions became, as they are today, white. Some of them, we thought, had atrophic scarring. There are no follicular changes.

The biopsy specimen does not show the atrophic changes that take place in that particular disease. However, the biopsy specimen was taken early, and we have been unable to take a biopsy specimen of the lesions after they have become white and waxy.

Dr. Cummer said that the appearance is not that of typical lichen sclerosus. That was the reason we presented it as a case for diagnosis. There are no subjective symptoms. These lesions come gradually, a few at a time. They have been rather slow, evolving to the point where there is an ivory color, which we think is scarring or a slight atrophic change.

I think that it is more than some type of atrophy. We could not make up our minds to call it Lecat's atrophic type, because I do not believe that it shows the histologic changes.

Pseudoxanthoma Elasticum. Presented by DR. E. W. NETHERTON and DR. W. R. HUBLER.

In C. M., an 8 year old white girl, there have developed numerous flesh-colored papules on the upper part of the trunk since August 1944. The initial lesions appeared suddenly over the sternum at that time. These lesions have not increased appreciably in size, but new solitary papules have continued to appear. All the lesions which appeared have persisted. There are no subjective symptoms.

There are two raised, flat, flesh colored nodules 5 cm. in diameter over the sternum. These show the remains of small papules at their peripheries. In addition, numerous flesh-colored, smooth, flat, round and linear papules 2 to 3 mm. in diameter are present on the arms and shoulders. Fine telangiectatic blood vessels course over the surface of all lesions. The papules become pink and edematous when scratched. No angioid streaks were present in the fundi.

There is no family history of a similar cutaneous disease. The patient's mother died of Addison's disease.

The hemogram was normal. The Wassermann and Kahn reactions of the serum were negative.

Histologic examination of a representative papule revealed separation and fragmentation of the bundles of collagen and moderate edema of the midcorium. A sparse perivascular lymphocytic infiltrate was also present in the corium. The epidermis was normal in appearance. Weigert elastic tissue stain revealed fragmentation of the elastic fibers in the midcorium.

DISCUSSION

DR. H. N. COLE: I do not think that I have ever seen pseudoxanthoma with the picture that this patient presents. These raised, firm lesions are different from those of pseudoxanthoma elasticum, which are little raised above the surface of the skin. It is only where the skin is under motion, usually around the arm or neck, that there is wrinkling of the skin so characteristic of the disease.

This is an infiltrated disease. While they do not have a tendency as yet to clear up in the center, I suggest granuloma annulare. On examination of the section of the tissue in the hematoxylin and eosin stain, there is one area in the corium that shows a localized cellular infiltrate much as is seen in granuloma annulare. There are no giant cells and no tendency to necrose in the center. Perhaps later, those changes will appear.

Moreover, on examining the section with the elastic tissue stain, I was not convinced there was enough breaking up of the elastic tissue fibers for pseudoxanthoma elasticum. Then, too, this child does not have any changes in the retinas. Of course, she is young, and, if it is pseudoxanthoma elasticum, angioid streaks may develop later.

DR. E. W. NETHERTON: I agree with Dr. Cole that this is an unusual type of this disease, but I believe that it is pseudoxanthoma elasticum. When we saw this child, we did not make the diagnosis clinically. The diagnosis was made on pathologic findings, confirmed by Dr. Harry Goldblatt and his associates. They think that it is histologically characteristic. That is one reason we accepted the diagnosis. The changes in the elastic tissue show decided fragmentation. It has been stated that the nodules, these large lesions, may start as papules. I believe that there are streaks commencing to develop parallel to the clavicle.

As for the histologic changes, there was practically no infiltrate except the one area Dr. Cole mentioned, but throughout the section there were fragmentation and edema. There was little cellular infiltrate in many sections taken out of one lesion that was about the size of the smallest papule and the largest on the chest. One would expect more inflammatory changes in some of these sections. The fragmentation of the elastic tissue I thought was severe and, for that reason, I think that we can accept the diagnosis.

Reticuloendotheliosis (Mycosis Fungoides?). Presented by DR. E. W. NETHERTON and DR. W. R. HUBLER.

Mrs. A. R., a white woman aged 50, was first seen at the Cleveland Clinic June 10, 1944, with a generalized, pruritic, vesicular and bullous eruption of one week's duration. She stated that she had had an erythematous eruption periodically for five years, which had partially cleared with roentgen ray treatment. She had taken no medicine and had not used local applications at the onset of the present eruption, but just prior to coming to the clinic she had received three intravenous injections of an unknown medicament and several roentgen ray treatments from her local physician, with no improvement. She was hospitalized. The eruption subsided with bland external treatment and hypodermic injections of sodium arsenate. A clinical diagnosis of dermatitis herpetiformis was made at this time. Two months later a generalized erythroderma was noted. This too was pruritic.

The eruption for which she is presented is similar to the initial eruption which she had several years ago. It consists of well defined, red, slightly raised, infiltrated, rounded and gyrate, slightly scaling plaques. The eruption is limited to the trunk and upper portion of the extremities. Numerous islands of normal skin

are surrounded by the erythematous plaques. No other abnormal findings were disclosed by physical examination.

Repeated hemograms in 1944 were normal, except for occasional abnormal lymphocytes. On July 9, 1944 the leukocytes numbered 4,650 cells per cubic millimeter, and the differential count showed 72 per cent neutrophils, 18 per cent lymphocytes, 1 per cent eosinophils and 8 per cent monocytes. There were no abnormal forms. The hemoglobin content was 78 per cent (12 Gm.), and there were 5,300,000 erythrocytes. The blood sugar level was normal. The total plasma protein content (Tiselius' method) was 5.72 Gm. per hundred cubic centimeters. The albumin content was slightly diminished (2.92 Gm. per cubic centimeter).

Sternal puncture was performed. A normal histologic picture was reported.

Histologic examination of a portion of a plaque from the right thigh showed a sharply limited, dense, cellular infiltrate in the papillary and subpapillary corium, which extended into the epidermis in some portions of the section, with the production of liquefaction degeneration. The infiltrate was composed of closely massed cells with scant vacuolated cytoplasm and large distorted nuclei with wrinkled nuclear membranes and a fine, basophilic internal pattern. Many had moderately enlarged nucleoli. An occasional mitosis was present. In some areas slender, collagenous bundles were present between the cells. Wilder stains showed a rich network of moderately coarse argyophilic fibers in the region occupied by the previously described lesion. There was intimal hyperplasia of some of the deeper blood vessels. Pigment was present in some of the areas of infiltrate.

DISCUSSION

DR. J. R. DRIVER: I think that the definite infiltration of these lesions suggests mycosis fungoides.

The process has been pruritic in the past, which would go with that disease. I do not think that it is a typical mycosis fungoides, but it looks more like that than anything else.

DR. W. R. HUBLER: When we saw this case, we felt that clinically it was typical of mycosis fungoides. However, on histologic examination, the cellular infiltrate is of such a uniform type that we felt that it did not fit with that picture at present, and the diagnosis of endotheliosis instead of mycosis, as suggested by Dr. Goldblatt, was accepted.

It is true that a good many of these conditions eventually turn into mycosis fungoides or one of the lymphoblastomas or sarcomas. It may be that in six months or a year we will change the diagnosis from reticuloendotheliosis.

I do not believe that the entity of reticuloendotheliosis is a clearly defined group. I feel, from the few cases I have studied and read about, that they usually develop into one or the other of the lymphoblastomas, so I can agree with Dr. Driver's suggestion of mycosis fungoides, at least as far as the future is concerned.

Superficial Epithelioma of Bowenoid Type. Presented by DR. SAMUEL AYRES III, DR. TOMAS GENATIOS and DR. WOODROW W. MURPHY.

M. P., a white man aged 70, is presented from the Department of Dermatology and Syphilology, Cleveland City Hospital, service of Dr. Cole and Dr. Driver. He had a persistent lesion of the left foot of ten years' duration.

On the dorsum of the left foot is a tender, irregular, slightly raised, ovoid lesion, 6 by 3 cm. in diameter, having a slightly moist, smooth, erythematous surface with white scales. Along one border are several confluent papules.

The Kline reaction of the blood was negative. The histologic examination showed acanthosis and parakeratosis. The basal layer of rete cells was sharply defined, and there was no evidence of invasion of the corium. There were many abnormal cells within the epidermis, some of which were multinucleated. The cells were large, and many showed disturbed polarity. Their nuclei showed variability of size, shape and chromatic content. There was a slight infiltration of lymphocytes in the superficial layer of the corium.

DISCUSSION

DR. ROY L. KILE (by invitation): When I first saw this lesion there was only an area of infiltration. I thought that it was irritation from his shoe, although it had lasted a long time. The resident prescribed soothing local application. After a biopsy was made, it was surprising to find that it was a superficial epithelioma. I think that one end of the lesion has become slightly verrucous in the last few months.

It has been my experience that this type of lesion does not usually respond to irradiation.

DR. J. R. DRIVER: This is a rare disease, and it is not seen often. I thought that it might respond to irradiation. Since that biopsy specimen was taken, about a year ago, the lesion has developed a papillomatous hyperplasia. A biopsy specimen now might show some penetration into the corium. It would be interesting to have a repeat biopsy specimen from the lower portion; then treatment would depend on what that biopsy specimen showed.

DR. W. R. HUBLER: Dr. Netherton and I have had the opportunity of seeing a number of cases that were somewhat similar and were histologically identical with this one. They responded well to superficial roentgen rays given with the Phillips x-ray therapy machine, which has a low kilovoltage and short target-skin distance. These lesions received 4,000 or 5,000 r.

DR. H. J. PARKHURST: Since there is some question as to the value of irradiation in this case, I should favor a thorough destruction with electrocoagulation.

Pinta. Presented by DR. SAMUEL AYRES III, DR. TOMAS GENATIOS and DR. WOODROW W. MURPHY.

W. T., a Negro man aged 55, is presented from the Department of Dermatology and Syphilology, Cleveland City Hospital, service of Dr. Cole and Dr. Driver. He complains of an eruption which began in 1926 with scaling of the palms, spreading to the dorsa of the hands and then to the flexor surface of the wrists, with hyperpigmentation, followed by depigmentation of a portion of the wrists. One year ago similar lesions developed on the thighs and legs.

He had a lesion on the prepuce in 1910, diagnosed as "chancroid" and treated only by circumcision. He was found to have a positive serologic reaction for syphilis in 1937 and received sixteen intramuscular and sixteen intravenous injections, at which time the eruption improved. No further therapy was given until November 1944, when the Kline and Kahn reactions of the blood were found to be positive. He received ten injections of oxophenarsine hydrochloride and one of bismuth subsalicylate. The eruption on the lower extremities, which was scaly, improved decidedly, according to the patient.

He was born in Tennessee, but since his youth he has spent most of his time in northern United States. He had never been outside the United States.

There is a slate gray, slightly scaly eruption with irregular, sharply defined borders present on the flexor surfaces of the forearms and the extensor surfaces of the legs and thighs, with discrete scattered lesions over the abdomen. On the flexor surface of both wrists are sharply defined, irregular areas of depigmentation. There are no sensory changes. There is some atrophy over the tibias. Small posterior cervical epitrochlear and inguinal lymph nodes are palpable. There is an aortic systolic and diastolic murmur.

The serologic reactions were:

	Wassermann	Kline Diagnostic	Kline Exclusion
November 1944	Not done	++	+++
February 1945	Negative	+	++
May 1945	Negative	++	++

The examination of the spinal fluid gave normal results. A differential count of the blood cells showed 5 per cent eosinophils. A roentgenogram of the chest

and cardiac fluoroscopy showed nothing abnormal. Repeated dark field examinations of the border of a hyperpigmented lesion revealed no spirochetes.

Histologic examination of a similar hyperpigmented area showed hyperkeratosis, a pigmented basal cell layer and large amounts of intracellular and extracellular pigment in the upper cutis. There was no evidence of inflammation.

DISCUSSION

DR. G. W. BINKLEY: I think that this is pinta. The man had spirochetosis, because there have been positive Kline exclusion and diagnostic reactions for many years. He had been treated with arsenicals and heavy metals. After such treatment the serologic reactions are weak, but there is a sufficiently high titer to make a diagnosis of spirochetosis even now.

Pardo-Castello and Ferrer, on pinta (ARCH. DERMAT. & SYPH. **45**:843 [May] 1942), stated that treated patients with pinta tended to be seropersistent, just as old syphilis is seropersistent when treatment is started late. "The Wassermann and Kahn reactions remain positive in many cases, in spite of the most intensive and prolonged treatment. In others, the reactions recede slowly and finally become negative."

In a case from University Hospitals which was presented before the Central States Dermatological Society (ARCH. DERMAT. & SYPH. **52**:415, 1945), the possibility of pinta was not thought of until after antispirochetal therapy was given, so a golden opportunity to prove pinta was lost. A proof of pinta as differentiated from syphilis is to take an old lesion like that on the forearm, draw serum and find the organism. The characteristic of Treponema carateum, or the pinta spirochete, is that it is supposed to be present in the skin as long as twenty or thirty years after infection takes place. Otherwise, there is no way to differentiate a pinta spirochetosis from syphilis. At present, the differential diagnosis must be made clinically.

From the dermatologic viewpoint, I have regarded these cases (the one presented today and the one presented before the Central States Dermatological Society) as pinta because the host's reaction to the spirochete differs entirely from late cutaneous syphilis as it has been known in the past. In a high per cent of late cutaneous pinta, persistent erythematous areas are present on the forearms and on the extensor surfaces of the legs. The erythema has a sharp border. The lesions remain red for years and develop hyperpigmentation, and finally areas of vitiligo appear. After antispirochetal therapy the erythema slowly fades, but the outline of the area can still be seen.

Perhaps some of you may have been impressed by the photograph of the Negro woman with extensive vitiligo (Fox, H.: ARCH. DERMAT. & SYPH. **40**:433 [Sept.] 1939). Vitiligo is variable and is often minimal. In Corpus Iconum Morborum Cutaneorum (Nékám, L.: Corpus Iconum Morborum Cutaneorum, Leipzig, Johann Ambrosius Barth, 1938, vol. 2, pp. 250-251), there are illustrated cases of pinta, with only a small triangular area of vitiligo on the flexor surface of the wrist such as this man has.

In addition to the vitiligo on the flexor surfaces of the wrists, this man has had the persistent erythema of his palms with hyperkeratosis. In the cases I have seen in Cleveland and in those which Leiberthal described in Chicago, it is usually present.

DR. J. E. RAUSCHKOLB: Dr. Tomas Genatios has pointed out that the history of this case goes back something like twenty-five years. During World War I, the patient was stationed throughout his Army duty at Fort Sheridan here in the states. He has never been out of the United States. He was discovered to have a positive Wassermann reaction shortly after the war and was treated. He might be one of the patients whose condition Leiberthal called pinta, for he came here from Chicago. Dr. Genatios thinks that this is a typical case of pinta.

When there were symmetric depigmentation and hypertrophic, increased pigmented, almost granular lesions at the peripheral border involving the lower extremities, that is, the medial extremities, he would diagnose pinta.

We did not find Treponema carateum. That is not always possible, although we should like to find it either in tissue section or by dark field search. The Kline test still elicits a positive reaction after twenty-five years' duration, so it can be regarded as a serologic-fast type of chronic syphilis or syphiloid or pintid type of Spirochaeta infection.

I traveled in Mexico searching for cases of pinta. There are supposed to be many cases of pinta in Mexico, but I found only 1 that was a counterpart of this.

Papulopustular Verrucous Sporotrichosis Simulating Blastomycosis. Presented by DR. E. W. NETHERTON and DR. W. R. HUBLER.

C. M., a white man aged 49, dates the onset of his present eruption about Dec. 10, 1944. At that time he pulled a couple of slightly infected hairs from the right nostril. In a few days the nose became red, swollen and tender. There was no itching. He consulted his physician, who prescribed sulfathiazole ointment for external use and sulfathiazole by mouth. Within a short time a generalized eruption developed necessitating the withdrawal of the use of the sulfonamide drug. The nose became larger. Small pustules developed on the surface of the distal portion of the nose, and later small papulopustules developed on the right side of the face, below the eye. The lesions on the face were acneform in type. There were no large, nodular lesions. He is a greenhouse employee and just prior to the onset of the eruption was working with mushrooms.

When this patient was seen for the first time, on March 28, 1945, there was a papulopustular, verrucous, crusted lesion involving the tip of the nose and extending upward to involve about two thirds of the nose. There were acneform lesions on the right side of the face, near the nasolabial fold and below the right eye. There was a small, soft, cystic lesion on the side of the nose, near the inner canthus of the right eye. The most intense reaction involved the tip of the nose, where the surface of the nose was verrucous and crusted. The lesion was not sharply demarcated, however, and there were many small, pinpoint pustules at the periphery of the lesion. The eruption has improved materially under treatment.

The acneform lesions have disappeared, leaving pink, slightly depressed scars. The tip of the nose is still erythematous, somewhat thickened and covered with a gray seborrheic scale. Pustules are not present now.

A section of the biopsy specimen which was examined March 29, 1945, showed some acanthosis and some liquefaction of the basal layer. In the papillary and subpapillary layers and upper portion of the corium there were numerous lymphocytes, large mononuclear cells, a few neutrophilic leukocytes and also a few plasma cells. A diagnosis of chronic granulomatous inflammation was made.

Cultures made March 28, 1945, showed a growth of Sporotrichum Schenckii. The identification of the organism was confirmed by Dr. Morris Moore, of the Barnard Free Skin and Cancer Hospital, in St. Louis. Wassermann and Kahn reactions of the serum were negative.

Treatment was use of saturated solution of potassium iodide N. F. by mouth and three roentgen ray treatments of 75 r each. He is taking 35 Gm. of potassium iodide after each meal.

DISCUSSION

DR. ROY L. KILE (by invitation): This case of sporotrichosis is different from either the localized lymphangitic or the generalized subcutaneous type. The former is usually caused by S. Schenckii and the latter by Sporotrichum beurmanni. Both usually respond rather promptly to therapy. This patient is also responding rapidly. The lesions are much more verrucous than those usually seen, and the location on the face is unusual. They are syphiloid in type and have ulcerated. One could not have made a diagnosis in this case without finding the fungus.

DR. E. W. NETHERTON: The features of this infection are the verrucous changes, the location and the fact that it does not fall into the customary nodular or gummatous type of sporotrichosis. The small pustules remotely simulated

blastomycosis. The lesions were sharply demarcated and had the distinct borders found in blastomycosis.

Papular sporotrichosis has been described recently by Costa and Junqueira (ARCH. DERMAT. & SYPH. **51**:261 [April] 1945). They reported a case of papular sporotrichosis with lesions on the nose. I recall reading reports a few years ago of sporotrichosis with lesions of this type on the hand.

Acanthosis Nigricans. Presented by DR. B. LEVINE.

A. G. is a white boy aged 16. A cousin of this patient has a similar eruption. Symptoms began a little over three years ago with increased pigmentation of the axillas and the groin. The patient has always been tall and obese. He is 6 feet 1½ inches (186.6 cm.) tall. There are areas of hyperpigmentation in both axillas, the neck, the groin, the inner surfaces of the thighs and the flexor surfaces of the elbows. In the pigmented areas, the skin is thickened with papillary hypertrophy, thus accentuating the lines of cleavage of the skin. The crests of the papillae are deeply pigmented, whereas the crevices show no pigmentation. There is no pruritus.

A culture of material from the axilla showed Staphylococcus albus and a type of Penicillium as a contaminant.

Histologic study of a section of skin showed the epidermis about average in thickness, with alteration of the epidermal cells. The upper layers showed considerable dyskeratosis, and there was an abundant layer of cornified cells covering the surface and filling numerous crypts which occur between interpapillary projections. The crypts are apparently unrelated to sweat glands or hair follicles. There was an increase in brown, granular pigment in the basal layer of cells. The corium was thickened by collagenous fibers and showed diminution in the number of sweat glands and hair follicles and increase in the number of capillaries, with moderate pericapillary round cell infiltration. In places there was increase in fibrous tissue about capillaries.

DISCUSSION

DR. H. J. PARKHURST: This boy has gained 100 pounds (45.4 Kg.) in weight over a three year period, and atrophic striae of the arms and trunk, as well as hyperpigmentation of the axillas, have developed. I feel that this may be a case of pituitary basophilism.

DR. H. N. COLE: I was inclined first to accept the diagnosis of juvenile acanthosis nigricans. However, he certainly has the build that would go well with pituitary basophilism.

DR. J. R. DRIVER: In view of what Dr. Parkhurst has said, it might be worth while to have an endocrinologist examine the patient for a possible pituitary disturbance.

DR. B. LEVINE: I do not think that it is pituitary basophilism. I do not know how else to classify this except as acanthosis nigricans. I did this for these reasons: There was papillary hypertrophy in the hyperpigmented areas, and the distribution of the pigment fitted typically with the description of the juvenile type of acanthosis nigricans. The ridges of the verrucous areas are pigmented, but the valleys lack pigment. An endocrinologist has studied the patient and found no endocrine dyscrasia.

A Case for Diagnosis (Quinacrine Hydrochloride Dermatitis). Presented by DR. H. G. MISKJIAN.

W. W., a white man aged 31 years, stated that in July 1944 there developed a pruritic eruption on the upper part of the thorax while he was serving with the armed forces in New Guinea. He had been taking quinacrine hydrochloride (atabrine) daily since March 1944. The eruption gradually spread to involve the face, hands and feet. In December 1944, administration of quinacrine hydrochloride was discontinued, and the patient was evacuated to the United States. En route

the eruption improved and has slowly regressed. The result of a biopsy performed after arrival was reported as lupus erythematosus.

Over the upper part of the chest and shoulders is a diffuse, mottled, erythematous and pigmented eruption with many tiny telangiectases and some areas suggestive of atrophy. On the occiput is an area of alopecia 3 by 2 cm. The scalp in this area is red and slightly depressed. The palms are thickened and have a mottled red color. On the right instep is a linear, red, scaly lesion with many fine telangiectases on its surface. There is a small keloid above the right breast, the site from which the previous cutaneous biopsy specimen was taken.

DISCUSSION

DR. H. HECHT: He has lesions on his feet that look like keratoses. I thought that the dermatitis was similar to arsenical dermatitis, so I asked him, "Did you take some pills or some tablets?" He said, "Yes, I was taking quinacrine hydrochloride." Since it improved after the use of quinacrine hydrochloride was discontinued, I think that it could be dermatitis due to quinacrine hydrochloride.

DR. H. J. PARKHURST: The erythematous patches on the extremities, scalp and upper eyelids, coming on rather suddenly as they did and fading out as they have, with atrophy remaining, suggests to me the possibility that this might have been a case of subacute disseminated lupus erythematosus.

DR. E. C. STERN: The lesions were not pruritic, and the atrophy, particularly on his neck and feet, suggests lupus erythematosus.

DR. H. N. COLE: I think that this man belongs in the group in whom this eruption has developed after they have taken quinacrine hydrochloride. It often looks like lichen planus, and in certain cases there may be some atrophy and a great deal of pruritus. There is much discussion about it yet, but probably it is secondary to the ingestion of quinacrine hydrochloride.

If they are unfortunate enough to get the combination which the boys call "jungle rot" (a bad term, which should not be perpetuated), which is a mycotic infection of the hands and feet, that completes the picture.

DR. H. G. MISKJIAN: The condition of this man has changed since the first examination. My first impression was that the eruption was a typical poikiloderma on the neck and the upper portion of the chest. There was diffuse redness and a peculiar mottled appearance. At the present time all that has disappeared. He has improved a great deal during the two months I have been able to observe him.

In this case, also, as in others, a diagnosis of lichen planus and of lupus erythematosus had been made, one by a well qualified dermatologist and the other by a man just as competent. To differentiate between the two, a biopsy was performed, but it did not lead to any definite conclusion. I do not have a report of the biopsy. There is a keloid on his chest, so I did not take another one.

First, in regard to lichen planus, I shall say that when I first saw this man there were definite papules on the wrist and anterior surface of the forearms, but a detailed examination of these papules made it obvious that it was not lichen planus. The papules had none of the features of lichen planus, such as the distinctive porcelain surface and similar aspects.

In regard to the diagnosis of lupus erythematosus, I think that it must have been suggested by the fact that the patient has a patch of alopecia on the occiput. That patch does not look like lupus erythematosus. It is a simple alopecia areata with a little redness, a slight depression and the ivory smooth texture of the skin. I do not think that there is any support for the diagnosis of lupus erythematosus because of the alopecia. It seems reasonable to incriminate quinacrine hydrochloride because poikiloderma-like lesions have been known to occur in other drug eruptions. In this case, if I am not mistaken, the patient began to take quinacrine hydrochloride in March, and his eruption developed in July. This would fit in well with the course of a drug eruption.

L. L. Praver, M.D., *President*

G. W. Binkley, M.D., *Secretary*

Sept. 27, 1945

A Case for Diagnosis (Lymphoblastoma?). Presented by Dr. Woodrow W. Murphy and Dr. Burt Held.

D. R., a 50 year old Negro man, complains of multiple soft tumors of the scalp of twenty-six years' duration. In 1919 he suffered from moderate pruritus of the scalp associated with the loss of scalp hair. About six months after the onset of pruritus, he noticed multiple papules in the pruritic areas. Slowly during a period of years these enlarged to form small nodules and plaques.

In 1922 the patient noticed a painless penile lesion, which healed in one month. At that time he received six intravenous injections. In 1941 the Kline and Wassermann reactions of the serum were found to be strongly positive, and he received a small amount of antisyphilitic therapy. Since April 1945 he has been treated with ten injections of 60 mg. each of oxophenarsine hydrochloride and ten injections of 130 mg. each of bismuth subsalicylate.

In December 1944 he was subjected to a subtotal gastric resection for a poorly differentiated adenocarcinoma with metastasis to the regional lymph nodes. Since the operation he has felt well, and no metastases have been demonstrable.

Examination of the skin reveals multiple soft, sharply defined, flat, skin-colored papules and nodules involving the temporal, parietal and frontal areas of the scalp and the periorbital areas of the face. In each parietal area the lesions have become confluent to form larger sharply defined, irregular, plaques, which show some atrophy of the overlying skin, with some loss of pigment. They are devoid of hair. These plaques are traversed by regular straight grooves that appear to be an accentuation of the normal lines of the skin and divide the plaques into multiple segments. The largest of these plaques is about 6 cm. in its largest dimension and is elevated about 5 mm. above the level of the skin. Examination of the lymph nodes reveals a few soft, bean-sized nodes in the inguinal, axillary and submandibular areas.

Roentgenograms of the chest showed no evidence of pulmonary infiltration. The hemogram and urinalysis showed normal conditions.

Histologic examination showed negroid skin. The epidermis showed no change of note. The corium showed a decided infiltration of cells of various types. The infiltration spared the papillary layer of the corium. The cells were seen in dense masses which had no relationship to blood vessels in the upper corium. In the deeper corium there was a moderate tendency for perivascular distribution. The commonest type of cell was fusiform to polyhedral with fibrillar processes and appeared to be related to the fixed tissues. The nuclei were oval to round and varied in amount of chromatin. Some of the cells were vesicular. Mitoses could be found after careful search. In some places, there were multiple nuclei in the cells, which nuclei tended to overlap. This differed from the ordinary Sternberg-Reed cell, however, in that those cells had more cytoplasmic processes. In addition to that type of cell, there were lymphocytes and eosinophils. Blood vessels showed decided proliferation, with obliteration of the lumen in some. Change in the blood vessels was greatest where the cellular infiltration was greatest.

DISCUSSION

Dr. Don R. Printz: Although the histologic changes of the disease varies, there is an infiltrate high up which suggests the possibility of a sarcoid. I thought of the Spiegler-Fendt type of sarcoid.

Dr. C. L. Cummer: I should like to ask the presenter whether he does not think that the diagnosis of lymphoblastoma is not inconsistent with the long duration, the twenty-five years the patient claims that he has had it.

DR. WOODROW W. MURPHY: That is correct. That is a rather long duration for lymphoblastoma. Lymphoblastoma was proposed because of the peculiar infiltrate, and the size suggested the possibility of mycosis fungoides. We welcome suggestions as to the diagnosis and as to therapy.

DR. E. W. NETHERTON: I agree that Dr. Cummer's point of the duration of the lesion is against lymphoblastoma. I thought that it was a sarcoid. Histologically, there is confusion. There is considerable fixed tissue reaction with the lymphocytes. The cellular infiltrate is localized in islands and nodular types separated by dense fibrous tissue. This would favor sarcoid; yet I do not think that it is histologically a sarcoid effect. I do not know just where to place it. I am trying to correlate the two findings and the histologic structure of sarcoid of some type.

DR. H. N. COLE: It would seem that this process might come under the heading of sarcoid. It is true that the man has no osseous changes, and I understand that roentgenograms of the chest show no evidence of sarcoidosis, but the histologic picture would go well with sarcoid. There are cellular masses with septums of connective tissue between them. I do not think that this process is deep enough for a Spiegler-Fendt type of sarcoid. That is supposed to be more in the subcutis, while this is definitely in the upper corium. If tuberculin tests have not been made I suggest that this be done. He might have an anergy, which would help in the diagnosis.

DR. E. W. NETHERTON: Was the biopsy specimen taken from one of the earlier lesions?

DR. WOODROW W. MURPHY: It was taken from an older, large lesion at the hair line.

DR. J. R. DRIVER: Have any of the lesions developed in the last year?

DR. WOODROW W. MURPHY: No.

DR. J. R. DRIVER: In talking with him, I got the impression that the disease has been much the way it is now for a number of years.

DR. WOODROW W. MURPHY: That is true. The history we obtained was that of no recent lesions. They have remained stationary for a number of years.

Psoriasis; Arsenical Pigmentation and Keratoses; Squamous Cell Epithelioma of the Finger with Metastasis to the Axillary Lymph Nodes.
Presented by DR. WOODROW W. MURPHY and DR. BURT HELD.

W. M., white man aged 49, entered City Hospital because of a fungating tumor of the finger. In 1940 a physician prescribed potassium arsenite for psoriasis. Since that time the patient has been obtaining the drug from a pharmacy without a prescription, and at the time of admission he was taking 45 drops a day. In 1942 the patient noticed hard, wartlike lesions on the hands and feet. In 1944, eight months prior to admission, he injured one of these lesions on the little finger on the right hand, and subsequently an enlarging fungating tumor developed.

Examination reveals a generalized grayish brown pigmentation of the skin, mottled with 2 to 4 mm. round areas of normal-colored skin. The pigmentation is greatest over the lower portions of the abdomen and back, the axillas, the cubital fossae and the pubic areas. The soles are covered with yellow hyperkeratotic papules and plaques varying from a few millimeters to several centimeters in diameter, which have developed since the destruction of similar lesions with the cautery in June 1945. The hands are covered with many hyperkeratotic papules varying from 1 to 5 mm. in diameter. There is a recent draining incision in the right axilla, made for a block dissection of the axillary lymph nodes.

The hemogram and urine were normal. The Kline and Wassermann reactions of the serum were negative. The urea nitrogen and sugar levels of the blood were normal. Roentgenograms of the chest were normal.

Histologic examination of the tumor of the finger showed large polygonal tumor cells of squamous cell type arranged in large sheets, with some tendency at the periphery to palisading. Whorls of tumor cells with pearl formation were present. Mitoses were moderate in number. No intravascular tumor was demonstrable. Histologic examination of a keratotic lesion showed hyperkeratosis and acanthosis of skin. Histologic examination of a section of pigmented skin showed melanotic pigmentation of the superficial corium. Histologic examination of a right axillary lymph node revealed a portion of a lymph node which was replaced by stratified squamous epithelial cells growing in compact masses. There were finger-like projections from the tumor cells. Four to five mitotic figures were present per high power field.

DISCUSSION

DR. R. E. BARNEY: This patient illustrates the danger of the prescription of arsenic for chronic diseases of the skin. This has been seen before repeatedly. I believe that Dr. Netherton stated about two years ago, when I showed a patient with the same symptoms, that he never uses arsenic for psoriasis.

DR. L. L. PRAVER: In a previous discussion Dr. Ormsby was quoted on the value of tablets of arsenic trioxide over potassium arsenite. Tablets of arsenic trioxide are not supposed to produce this type of reaction.

DR. H. N. COLE: When patients are given a prescription for potassium arsenite and the druggist says, "Oh yes, potassium arsenite," then patients learn the name. The patient immediately follows that up and asks for potassium arsenite over the counter, and it is sold occasionally. If one prescribes liquor acidi arseniosi U. S. P., it is not easy to remember and to repeat.

Lichen Planus with Involvement of the Palms. Presented by DR. WOODROW W. MURPHY and DR. BURT HELD.

M. B., a white man aged 73, complains of pruritic lesions of the hands, feet, axillas and groins of five months' duration. Lesions were first noticed on the hands and were associated with severe pruritus. In about six weeks the palms had become covered with lesions and new ones appeared on the dorsa of the hands, the ankles, axillas and groins. When first seen, the palms of the hands were covered with many, hard, 3 to 4 mm., yellowish white, umbilicated, globular, flat-topped papules. He was treated with three weekly injections of 130 mg. of bismuth subsalicylate. The last injection was given Sept. 6, 1945.

Examination reveals the palms to be erythematous and also to be covered with many close, 2 to 3 mm., yellowish white, slightly elevated flat papules. Scattered around the borders of the fingers and palms are 3 to 5 mm., yellowish white, umbilicated, flat-topped papules covered with a thin translucent scale. On the dorsa of the feet and hands and on the wrists are typical violaceous, angular, flat-topped papules, some of which are arranged in a linear fashion. In the axillary region and groins are multiple discrete linear, flat-topped, violaceous, pruritic plaques averaging approximately 2 cm. in diameter. On the right buccal mucosa there is a slightly erythematous lesion covered with fine retiform bluish white lines 3 cm. in diameter. An anterior segment has been removed for histologic examination.

The Kline and Wassermann reactions of the serum were negative. The hemogram and urine were normal. A roentgenogram of the chest was normal.

Histologic examination of a papule from the wrist showed moderate hyperkeratosis. The epidermis was hyperplastic in one area, and below it was a superficial dense lymphocytic infiltration. There was moderate edema in the papillary and subpapillary layer. Capillaries and histiocytes were more numerous than usual.

Histologic examination of a papule from the palm revealed hyperkeratosis, which, the site of the lesion being considered, was normal. There was no acanthosis. There was separation of the epidermis from the papillary corium in places. There was a moderate superficial lymphocytic infiltration.

Histologic examination of the lesion from the right buccal mucosa revealed a specimen which appeared to be cut obliquely to the surface, giving the mucosa unusual breadth. Keratinization was slight. There was an infiltration of lymphocytes limited to a narrow zone just beneath the epithelium.

DISCUSSION

DR. E. C. STERN: Six months ago I saw a girl with lichen planus. Later her father came with lichen planus on his hand, the same disease. It spread to his entire skin. I do not know whether there is any connection between the 2 cases. The daughter was cured in three or four months.

DR. L. L. PRAVER: If this man becomes resistant to bismuth therapy and other treatment, I suggest the use of vitamin A. Dr. Obermeyer presented a case before the Los Angeles Dermatological Society in which hypertrophic areas responded to large oral doses of vitamin A.

DR. J. R. DRIVER: Several years ago Dr. Cole and I saw a patient with extensive lichen planus involving the mouth. He also had lichen planus of the palms. The eruption cleared up after a few months of treatment. His sister came in several years later with the same disease. I wonder if others have seen such cases when there are more than one in the same family.

DR. J. E. FISHER: Recently I had 2 sisters with lichen planus under my care. They gave a history of the appearance of lesions after their mother died.

Larva Migrans. Presented by DR. DON R. PRINTZ for DR. H. N. COLE and DR. J. R. DRIVER.

B. F., a white man aged 55, was first seen on Sept. 12, 1945, complaining of an eruption on the right calf which started as a red pimple that itched intensely. The patient had been in Florida in June 1945, and it was soon after this that the pimple appeared, but not until four weeks ago did it start to spread. There was some tenderness and at times pain.

Examination shows a fine pencil-like lesion on the right calf that extends in a gyrate pattern. The lesion is slightly elevated above the surrounding surface and has the appearance of containing vesicles along its course. One might compare the lesion to the trail left by a burrowing ground mole. There are some redness and edema along the course of the eruption. There are also three crusted areas, which have been painted with gentian violet medicinal. These are the results of ethyl chloride spray applied to the lesions.

Treatment has been three intramuscular injections of small doses of fuadin.

DISCUSSION

DR. DON R. PRINTZ: Dr. D. C. Smith, of the University of Virginia, published an article several years ago in *The Journal of the American Medical Association* (**123**:694 [Nov. 13] 1943) about the use use of antimony preparations in larvae and similar infections. Dr. Wilson of Jacksonville, Fla., started to use fuadin in creeping eruption. His first dose was 5 cc. daily for five days, but he found out by gradually reducing the dose that that amount was not necessary. He reduced the dose to 5 cc. repeated in one week, and his results were still good. In only 1 patient out of 10 that he treated did he have any trouble, and in children up to 8 years old only 1 cc. was required (Wilson, J. F.: Treatment of Creeping Eruption with Fuadin, J. Florida M. A. **30**:425, 1944). In this case we injected only 1 cc., and the larva was dormant for five days. Previous to that, it had been moving every day. If 1 cc. would do that, probably 5 cc. would be lethal.

DR. J. E. FISHER: In addition to fuadin what other type of treatment is effective?

DR. H. N. COLE: In the past, therapy has been freezing with either ethyl chloride or solid carbon dioxide. If one is lucky enough to catch the place where the larva is, that will take care of it. One may or may not get the right place. The result does not show up for some time. The family physician had seen this

patient, made the correct diagnosis and treated him with ethyl chloride but did not freeze the larva.

Dermatosis, Progressive Pigmentary. Presented by DR. DON R. PRINTZ for DR. H. N. COLE and DR. J. R. DRIVER.

B. G., a white woman aged 19, was seen on Sept. 6, 1944, complaining of brown spots on her legs, of about two years' duration, which had appeared after she had received a bruise on the right leg. The lesions have increased in number and progressed downward. The same lesions are appearing on the left leg. She states that she has a tendency to bruise easily.

Examination reveals small, discrete, burnt orange–colored lesions with irregular borders, some of which are confluent. They are distributed over the lower anterior and lateral aspects of the right leg. Similar lesions are to be found in the region of the left ankle. The lesions blanch a little under pressure, and there is no follicular involvement. No signs of hemorrhagic diathesis are present. Physical examination otherwise gives essentially normal results.

The hemogram and urine were normal. Kline diagnostic and exclusion tests of the serum elicited negative reactions. The prothrombin level was 82 per cent of normal, and a repeated test, two days later, was 75 per cent of normal by Quick's method. Bleeding time was one minute and fifty-five seconds and clotting time three minutes and fifty seconds. The blood urea nitrogen level was 12 mg. per hundred cubic centimeters; urea clearance was normal. The Rumpel-Leede test gave essentially normal results.

Histologic examination of skin from the leg revealed considerable hyperkeratosis with some thickening of the stratum mucosa. In the upper portion of the dermis were large mononuclear cells and some lymphocytes. There were also scattered erythrocytes and phagocytes containing granular light brown pigment in the upper dermis. Sections treated with hydrochloric acid and potassium ferrocyanide showed a large amount of iron-containing pigment in the dermis.

DISCUSSION

DR. H. G. MISKJIAN: This might be called cutaneous hemosiderosis, a limited type. Such conditions have been proved to be of capillary origin, as can be seen clinically. They should be called a type of capillaritis. In fact, if there is any pure type of this, the histologic structure of progressive pigmentary dermatosis shows it. These capillary changes bring the disease into the large group of cutaneous disease due to capillaritis.

Myoblastoma. Presented by DR. DON R. PRINTZ for DR. H. N. COLE and DR. J. R. DRIVER.

N. M., a white man aged 71, was seen first on April 10, 1945, complaining of a white spot on the tongue, of about three weeks' duration, which rubbed against his teeth and became slightly tender after he smoked his pipe.

Examination revealed a small, dull white, indurated lesion, 6 mm. in diameter, on the left side of the tongue, slightly toward the ventral aspect, 3 cm. from the tip. It had the appearance of a leukoplakia that was slightly elevated above the surrounding mucous surface.

With the patient under local anesthesia the entire lesion was excised for histologic examination. There was slight superficial hyperkeratosis. The mucosa showed a decided acanthosis with a pseudo epitheliomatous hyperplasia. There was no invasion even though there were small keratin pearls deep in the epithelium. Little inflammatory infiltration was seen. Extending from the epithelium to the deeper muscle and infiltrating into the striated muscle fibers were large pale staining cells with small nuclei and granular cytoplasm. These cells resemble xanthoma cells, but stains for fat were negative. In some places these cells appeared to be degenerated muscle fibers.

DISCUSSION

DR. DON R. PRINTZ: There are only about 75 or 80 cases reported in the literature. There have been several complete articles in the *American Journal of Cancer*. Dr. Klemperer stated (Am. J. Cancer **20**:324 [Feb.] 1934) in his review that about 44 per cent of all the cases are of the tongue and the rest are of the esophagus, the mouth and some of the trachea. An interesting thing to note in this is that it looked like a leukoplakia. In looking at the biopsy specimen, one saw a hyperplasia which might be mistaken for a bit of malignant growth. Stains of these xanthoma cells, as was noted in the write-up, were negative for fat. They contained no fat, and in looking at the cells more closely, one found that they were coarse and granular and took neutral stains. The cytoplasm was faint staining. The muscle seemed to be degenerated striated muscle. The theory offered by Elrikossoff was that they were the result of injury. Of several other theories offered, one considered the lesions neoplastic. However, none of them have been malignant, except in 1 case that was one of sarcoma. It was reported in the literature as myoblastic. The treatment is simply excision and cautery.

DR. J. E. FISHER: What was the diagnosis before the excision was done?

DR. DON R. PRINTZ: The clinical diagnosis was leukoplakia with a possible malignant change.

DR. J. R. DRIVER: The lesion was more yellowish, and it was sharply delimited and raised a little more than one would expect of an area of leukoplakia. He had no other leukoplakia in his mouth. It looked like a little area of leukoplakia with xanthomatous degeneration. It was only after the histologic examination that the diagnosis was made.

A Case for Diagnosis (Epidermolysis Bullosa?). Presented by DR. WOODROW W. MURPHY and DR. BURT HELD.

R. W., a 17 month old white boy, was seen in September 1945, because of a recurrent bullous eruption of the hands and feet. The lesions first appeared at the age of 5 days and have recurred about every three months since. New lesions appear for two to three weeks, remain for four or five days and then disappear by absorption of the bulla fluid. The mother has been treating them by rupturing the bullae as they form and applying solution of gentian violet medicinal to the base. The lesions are apparently asymptomatic. The formation of the bullae is not related to trauma.

There is no family history of similar lesions.

On the palmar surface of the fingers and hands and on the lateral side of one toe of the right foot are multiple thick-walled bullae 5 to 10 mm. in diameter, containing a clear fluid. These lesions arise from apparently normal skin, with no evidence of surrounding inflammatory reaction. There is no evidence of disease of the nails.

A roentgenogram of the chest was normal. The hemogram and urine were normal. The Kline diagnostic and exclusion reactions of the blood were negative.

Histologic examination showed a strip of hyperplastic epidermis and in one small area a little superficial corium. There was moderate hyperkeratosis. The corium showed an infiltration of lymphocytes and edema. There was splitting at the junction of the epidermis and corium. Elastic tissue stains showed no fibers in this area.

DISCUSSION

DR. H. N. COLE: I do not think that it is epidermolysis bullosa. In epidermolysis that has lasted as long as this, one would expect to find some milia in the area where the child is accustomed to have these lesions, and I could not find any at all. I am sure that I do not know what it is. Perhaps it might be a type of pustular mycosis. I do not think that it is epidermolysis bullosa.

DR. J. R. DRIVER: The disease started when the child was 6 days old and has been present ever since.

DR. J. E. RAUSCHKOLB: The history obtained from the mother on the child's admission was that the child had lesions that were typically bullae on the exposed parts, particularly the hands and the area of the ankles. When examined last week there were two or three soft bullae that did not have a red or inflamed border. No one else in the family as far as she knows—the grandparents or her family or the sister or brothers of this child—have had any lesions like this. These lesions have been present periodically almost since birth; therefore we thought that probably this was one of the recessive type of epidermolysis bullosa. Clinically at the time we saw it, it certainly was not a dermatophytosis with the vesiculated border; there were clearcut bullae, unfortunately not present today.

PHILADELPHIA DERMATOLOGICAL SOCIETY

J. M. Schildkraut, M.D., *Chairman*

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Sept. 21, 1945

Actinomycosis. Presented by DR. FRANK C. KNOWLES.

S. C., a white man aged 38, presents depressed, pigmented and granulating lesions of the anterior region of his thighs. Pigmented scars of healed lesions are present on both legs. The patient was admitted to the hospital on Sept. 15, 1943, with a draining sinus of the right side of the face and spasm of the right masseter muscle. This followed incision and drainage of an abscess of the right cheek after apical infection of an upper molar on the right side in June 1943. Metastatic abscesses then developed in the extensor muscles of the forearms, followed by abscesses in the right temporal region. On Nov. 15, 1943, he was readmitted to the hospital with multiple abscesses of the extensor surfaces of the thighs, the left gluteal region and the right supraclavicular region. During this time a gluteal abscess and uveitis developed. He was discharged on March 1, 1944, and readmitted on March 7, 1944, complaining of pain along the lower intercostal nerves.

Roentgenographic studies of the chest revealed infiltration of the pulmonary fields. A bacterial smear showed Actinomyces, and a culture revealed Actinomyces bovis. Two white cell counts of his blood recently performed revealed 9,450 and 8,200 cells respectively. The sedimentation rate of the blood on April 27, 1944, was 35 mm., and in September 1945 it was 19 mm. The histologic report was "chronic inflammation."

On Nov. 5, 1943, the areas were incised and drained. The patient was given injections of penicillin on Dec. 3, 1943 (10,000 units every four hours).

DISCUSSION

DR. DONALD M. PILLSBURY: Has there been improvement since administration of penicillin was started? I have not seen any patients with actinomycosis treated with penicillin, but my impression is that those who responded had received larger doses. I think also that this patient may demonstrate possibly, if he has an abscess of any sort, that the use of penicillin alone, without surgical drainage of the abscess, may not be entirely effective. The diagnosis in this case is clinched.

DR. JOHN F. WILSON: In spite of many tissue sections over a period of three years, not a single specimen showed actinomycosis. Cultures finally revealed the organism.

DR. ISADORE ZUGERMAN: I should like to suggest the use of streptomycin.

Annular, Macular Syphilid. Presented by Dr. Fred D. Weidman and Dr. Simon Katz.

T. G., a Negro woman aged 40 years, presents on her chest irregular circular and oval rings with clear centers and also segments of circles which by coalescence form gyrate figures. The lesions have crinkly borders, are slightly scaly and show no infiltration. One week following her discharge from the hospital a month ago, following an operation for gallstones, the patient noticed a number of dark areas on both sides of her chest. A week later oval lesions appeared in the same regions.

The Wassermann reaction of her blood on Sept. 10, 1945, was strongly positive. On Sept. 14 and 18, 1945, she received an intravenous injection of 0.3 Gm. and 0.45 Gm. of neoarsphenamine respectively.

DISCUSSION

Dr. J. V. Klauder: I do not agree with the diagnosis. I think that it is parapsoriasis. My concept of the annular macular syphilid is that it is never a scaly lesion and never a diffuse lesion such as this. It must be an extremely rare disease; I have seen only 1 case in many years of observation. I should like to know on what basis the diagnosis was made. My concept is that it is always a rather localized, not diffuse lesion.

Dr. Fred D. Weidman: Dr. Katz and I knew that we would have repercussions on this. Frankly, we did not feel that it was a case of so-called neurosyphilid, but we thought that that was the best way of securing a discussion of it—to throw out the challenge. This is not a diffuse eruption. The lesions are annular. Our first thought was that it might be a form of erythema multiforme, such as erythema perstans or the erythema chronicum migrans of Lipschutz, but the drawback to that was that there are definite atrophic pittings in the margins of these lesions, which seem to indicate a heavy degree of infiltration. Furthermore, against the idea of neurosyphilid is the fact that this eruption is bilateral and symmetric. So we were torn between these considerations. I have seen only 1 case of Unna's neurosyphilid; I think that Dr. Klauder saw it, too, at a meeting of the American Dermatological Association in Washington, D. C. It was presented as a case of leprosy, and then some one advanced the diagnosis of neurosyphilid of Unna. The eruption consisted of a solitary lesion on the chest. In that case there was not the degree of infiltration in the periphery that has been present in the early stages of this lesion. Dr. Katz and I should like suggestions as to what this may be.

Dr. Vaughn C. Garner: I may be wrong, but it seemed to be my impression that the neurosyphilid of Unna involves changes in the nerve supply of the skin rather than a definite connection with syphilis of the central nervous system. Is it not true that this patient has had two treatments for syphilis? Has there been any clinical improvement since treatment was instituted?

Dr. Simon Katz: We have not noticed any change.

Keloids. Presented by Dr. Meyer L. Niedelman.

N. W., a white woman aged 24 years, presents on the dorsum of the left wrist a round, marginated, elevated, irregular, erythematous and hard keloid measuring 3.5 by 4.5 cm. It is raised about 1 cm. above the surface. The lesion interferes with free mobility of the wrist. Behind the left ear there is a keloid extending along the line of incision from which a skin graft was taken some time ago. The patient had a small ganglion of the dorsum of the left wrist. It was removed by operation in March 1944. Shortly thereafter, a keloid about the size of a dime developed at the site, with impairment of motion of the wrist. In May 1944, the keloid was excised surgically and the area covered with a graft from the left retroauricular region. Shortly thereafter, the present keloid developed on the wrist. It is accompanied with much itching and pain. A keloid formed at the donor site in the retroauricular area.

The patient received one roentgen ray treatment, 225 r with 3 mm. aluminum filter, a week ago.

DISCUSSION

DR. A. STRAUSS: I believe that Dr. Pfahler advises surgical excision of keloids and the use immediately after the operation of 400 r with a 1 mm. aluminum filter, to be followed within a week with 300 r and repeated in another week.

DR. MEYER L. NIEDELMAN: I believe that the surgeon erred originally in not following the graft up immediately with roentgenotherapy. I believe now that roentgenotherapy is the method of choice.

DR. A. STRAUSS: Dr. Pfahler has stated the belief that if plastic surgical treatment is to be done it should be done afterward.

DR. J. M. SCHILDKRAUT, Trenton, N. J.: Sometimes keloids respond well to roentgenotherapy.

DR. THOMAS BUTTERWORTH, Reading, Pa.: Has any one ever destroyed keloids of this size with solid carbon dioxide? I have removed small ones by this means.

Ulcers: Acute Pyogenic (?) Factitial (?) Anaerobic (?). Presented by DR. FRANK C. KNOWLES.

O. D., a white woman aged 23, presents on the right forearm a granulating ulcer about 1 cm. in diameter, extending into the subcutaneous tissue. A similar but larger ulcer is present on each gluteal region. The lesion on the right forearm appeared several weeks ago, while the patient was receiving treatment with penicillin.

About three months ago headaches, fatigue and malaise developed. On Aug. 17, 1945, her temperature was 101 F. She was admitted to the hospital five days later. There a sore throat developed. She has lost 20 pounds (9 Kg.) in the last year. She had phlebitis of the left leg during the last month. Her temperature, which has ranged from 99 to 104 F., has been normal since September 9.

A blood cell count revealed a 67.3 per cent hemoglobin content, 3,700,000 erythrocytes and 13,350 leukocytes. Bacterial culture of the vesicles showed Staphylococcus aureus and Staphylococcus albus. The patient's serum agglutinated Eberthella typhosa in dilutions of 1 to 20 and 1 to 640.

The patient received 150,000 units of penicillin.

DISCUSSION

DR. DONALD M. PILLSBURY: The ulcer on the forearm is entirely compatible with diphtheria cutis, an entity with which I was unfamiliar before seeing it in the Army. There was a great deal of diphtheria in the South Pacific area, particularly in Saipan, much more than in the European Theater of Operations. The lesions are frequently sharply punched out, like this one, may be deep and may or may not have sequelae. Sometimes the sequelae are severe. I recall seeing 1 patient with a penile diphtheritic ulcer, in a hospital in England, who died of myocardial disease. It may or may not be possible to demonstrate the organism. The results of the Schick test are variable. I think that it should be attempted here. These patients will, of course, improve decidedly with penicillin therapy, local or otherwise. Livingood and others have expressed the opinion that repeated formation of a bulla on a healed scar is highly characteristic of diphtheria cutis.

DR. J. V. KLAUDER: Are the diagnoses positive in cases in which the organism is not demonstrated?

DR. DONALD M. PILLSBURY: It has been necessary to make a presumptive diagnosis in many cases. There have been many instances of myocardial sequelae and peripheral neuritis in such cases. There is a particular tendency toward diphtheria of the skin in the hot climates. It developed frequently in German prisoners, possibly because diphtheria toxoid immunization is rarely used in Germany and the general resistance of the German population to diphtheria is low. These cutaneous lesions do not respond particularly well to diphtheria antitoxin. It is given primarily to prevent sequelae, but treatment with salt solution and with penicillin are the methods of choice. The scar of cutaneous diphtheria is one of the most sharply punched-out scars that one sees—more so than syphilis.

Malignant Melanoma. Presented by DR. FRANK C. KNOWLES.

A. A., a white woman aged 59 years, presents on the posterior portion of the right arm, in the right axilla, in the right upper scapular region and on the abdomen various-sized, firm, slightly tender subcutaneous tumors. One on the left side of the abdomen is grayish black. The patient, a cachectic woman, noticed pain in the left lower quadrant about five weeks ago. She then found a lump in the skin in this area which was hard and tender. There is a similar lesion on the posterior part of the right arm. Three weeks ago a dark lesion (black?) appeared under the right axilla and later on the right upper scapular region. This was followed by pain in the right breast, radiating to the back and down the right arm; it gradually became worse.

A blood cell count revealed a 55.4 per cent hemoglobin content, 2,700,000 erythrocytes, 5,100 leukocytes, 308,000 platelets, 75 per cent segmented polymorphonuclear leukocytes, 16 per cent medium and small lymphocytes, 6 per cent monocytes and 3 per cent disintegrated cells.

Dr. G. P. Muller surgically removed a well encapsulated mass, about 4 cm. in length and 3 cm. in diameter, from the right axilla, lying deep in the tissue along the axillary artery and vein. The mass was opened and found to be filled with a blue-black colloidal material.

The histologic diagnosis on the biopsy specimen was malignant melanoma.

DISCUSSION

DR. BERNARD L. KAHN: How would one make the diagnosis clinically, without a biopsy?

DR. J. M. SCHILDKRAUT, Trenton, N. J.: I do not know that one could make the diagnosis clinically. It might be suspected if the patient was losing weight and becoming cachectic. Perhaps the color of the lesion might arouse suspicion.

A Case for Diagnosis. Presented by DR. DONALD M. PILLSBURY and DR. E. R. CONSTANT.

A white woman aged 44 years gives a history of the development of inflammatory papules and nodules all her life, usually on the neck, which would last from several months to a year. Some disappeared spontaneously, and others would have to be incised by herself or her husband and after draining would heal with scar formation. At the time the patient was first seen, July 9, 1945, she presented a nodule about 1 cm. in diameter on the anterior aspect of her neck and also several smaller, nonfluctuating papules. Around the neck were a number of white, noncontractile scars with bizarre borders. Scars of previously removed lesions (1943) were noted over the right mandible (no report of biopsy available), on the posterior aspect of the right thigh (report of biopsy: lipoma) and on the left breast (report of biopsy: chronic cystic mastitis).

The nodule on the neck was excised, and the following histologic report was submitted by Dr. Fred D. Weidman:

"Speaking collectively, from the two halves of the lesion which appeared in the section, it was clear that an invaginated pocket of dense hyperkeratotic material occupied the summit of the lesion; incidentally, the keratotic material extended also into the orifices of some of the hair follicles.

"The entire epidermis was acanthotic and extremely irregular in the extent to which extensions pass from it into the corium. Indeed, some of them extended to the bottom of the section. Some of them appeared in the form of epithelial pearls.

"The stroma did not contain nearly so much lymphocytic infiltration as might be expected. The large numbers of dilated capillaries in the stroma were most unusual, so much so as to suggest that the lesion came from some highly vascular region like the lip. However, these vessels were not arranged in a fashion that is consistent with a hemangioma, but it is granted that they might represent a mild expression of vascular nevus. There was not the slightest evidence of formation

of a granuloma or other process that would seem to demand tests for bacteria. This lesion was an extremely slowly proliferative precancerous dermatosis that had passed over into malignant change of low grade. One cannot escape the diagnosis of a malignant growth with the pearly bodies lying at such a deep position, to say nothing of the active type of cell that is concerned in the other squamous cell infiltrations. This is the kind of cancer that I should expect to develop as the result of exposure to carcinogenic agents such as tar and which are known to regress spontaneously.

"The pathologic diagnosis was precancerous dermatosis with malignant change."

The following examinations and tests were performed and found to give results within normal limits: blood cell counts, urinalysis, basal metabolic rate, blood sedimentation rate and roentgenographic studies of the chest, abdomen and gastrointestinal and urinary tracts.

Smears and cultures of material from the removed gland were negative for tuberculosis or fungi. Bacteriologic studies were made both aerobically and anaerobically, and hemolytic Staph. aureus was found in moderate numbers, a few short chain indifferent streptococci were found and a large colony of Streptococcus fecalis type was present.

The patient reacted moderately to 0.1 cc. of staphylococcus ambotoxoid diluted 1:10 with isotonic solution of sodium chloride. She has received no active treatment.

DISCUSSION

DR. J. V. KLAUDER: I suggest acne urticata as a possible diagnosis.

DR. FRED D. WEIDMAN: I wish that I could reconcile the clinical picture with the one that I saw in the section. I made a report of precancerous dermatosis from what I saw. There must have been an additional lesion much larger than any appearing tonight, and that was sent to me for study.

DR. DONALD M. PILLSBURY: You were seeing a late development of the process.

DR. FRED D. WEIDMAN: I reviewed the section this afternoon. Ordinarily I should call the process a pseudoepitheliomatous hyperplasia, but I could not see the suppuration which is almost invariably present in that condition, and that is why I did not mention it in the original pathologic report. Joining up what I have seen tonight with the sections, I should say that probably the sections have no diagnostic significance but exhibit simply an active attempt at regeneration of the skin.

DR. HERBERT J. SMITH: I agree with what Dr. Klauder said. I think that we all see these small, multiple, scarlike lesions which do not seem to amount to anything at all. We often find that such patients do have what the patient describes as a recurrent summer eruption, that is, lichen urticatus.

DR. J. V. KLAUDER: I should suggest that this woman be given calcium therapy. I have thought that patients were benefited by such therapy. There is also a factitial element about this picture. The original lesions which she had were aggravated by picking after they appeared, which added to the scar formation. Lichen urticatus is too briefly described in modern textbooks for one to get an intelligent concept of it. It is best described in some of the older European textbooks, and the best description is the original one by M. Kaposi (Ueber einige ungewöhnliche Formen von Acne [Folliculitis], *Arch. f. Dermat. u. Syph.* **26**:87, 1894). A discussion of this disease is also afforded by J. V. Klauder and F. D. Weidman (Acne Urticata Polycythaemica; Positive Oxidase Reactions in Lesions Macroscopically and Microscopically, ARCH. DERMAT. & SYPH. **39**:646-666, 1939).

DR. JOHN F. WILSON: I first saw this girl a year and a half ago. She then had two or three superficial excoriations of the skin. There was nothing typical about the eruption. It seemed to me that she made more of it than was really there. Looking back, it certainly does seem to fit in with acne urticata. There is a definite element of neurotic excoriation to it. She certainly traumatizes the lesions; she frankly admits it.

A Case for Diagnosis (Lupus Vulgaris?). Presented by DR. SIGMUND S. GREENBAUM.

M. Y., a white woman aged 24 years, an average normal woman, intelligent and cooperative, presents on the right cheek a more or less circumscribed erythema with slightly visible and definitely palpable nodules, some of which are dark brown under glass pressure. There are no subjective symptoms. On the left side of the chin there is a scaly, well defined, pink, nickel-sized, nonpruritic area. The eruption is of two years' duration. It began as a small red papule on the right cheek. No treatment was given. It gradually spread to its present size. A smilar lesion appeared on the left side of the chin two months after the original lesion. This was treated with ultraviolet irradiation a few months ago by a dermatologist. There is no pruritus.

The patient's mother is living and well at the age of 49 years, as is her father, at the age of 53 years. She has two brothers, aged 27 and 22 years, and a sister 15 years, all living and well. There is no history of the eczema–hay fever–asthma complex in the family. The patient has had the usual childhood diseases, including parotitis, and a tonsillectomy in 1938. She had a premature delivery, at seven months, of a stillborn child in 1944. She has gained 5 pounds (2.3 Kg.) in the past two years.

A reaction to the patch test for tuberculosis and the serologic reaction of the blood for syphilis were negative. A complete blood cell count and a urinalysis gave normal findings.

DISCUSSION

DR. BERNARD L. KAHN: I make a diagnosis of rosacea.

DR. MEYER L. NIEDELMAN: I think that it is the Lewandowsky rosacea-like tuberculid. No pustules are present; the lesions are not centrally located, and no seborrhea is present. I should suggest an intradermal tuberculin test, which would aid in establishing the diagnosis.

DR. ISADORE ZUGERMAN: I found some follicular plugging present. I suggest the diagnosis of subacute lupus erythematosus.

DR. VAUGHN C. GARNER: I favor the possibility of a rosaceaform tuberculid, from a clinical standpoint.

DR. DONALD M. PILLSBURY: I think that it is of interest that the lesion on the left side of the chin was apparently similar to that on the right cheek. It would be well to have a biopsy. I should consider treatment with solid carbon dioxide.

DR. FRED D. WEIDMAN: There is a deep-seated nodule at one place. If that occurred by itself, all of us would think of some condition of the sebaceous glands, perhaps a sebaceous cyst. I do not think that this is Lewandowsky's tuberculid; those are generally diffuse, while this is well confined to one area.

DR. J. V. KLAUDER: It impressed me as Lewandowsky's tuberculid. I do not know that the statement that it is too localized would exclude the diagnosis.

Hemangioma. Presented by DR. ARTHUR G. PRATT, Camden, N. J.:

V. S., a white boy aged 6 years, on examination on May 16, 1939, presented a massive, elevated, ruby red hemangioma encircling the left forearm and covering the back of the left hand.

A roentgenogram on Dec. 16, 1943, showed no disease of the bones of either forearm or hand.

Radium, to a total of 50 mg. hours, was administered from June 7, 1939, to Oct. 26, 1940. A total of twelve injections of quinine and urea hydrochloride was given from Dec. 21, 1939, to Jan. 30, 1941. There has been a good cosmetic result.

DISCUSSION

DR. ARTHUR G. PRATT, Camden, N. J.: The reason for presenting this case was to try to get some discussion concerning the therapy of strawberry marks.

Some are thought to disappear spontaneously, without any treatment or with little treatment.

DR. MEYER L. NIEDELMAN: Anderson, in a recent article, claimed that 90 or 95 per cent of angiomas will disappear spontaneously before the sixth year. As to injection therapy, at the last meeting of the American Academy of Dermatology and Syphilology a death was reported in an infant due to cerebral thrombosis following injection with sodium morrhuate. I prefer the use of radium or solid carbon dioxide.

DR. THOMAS BUTTERWORTH, Reading, Pa.: Large lesions may be treated by roentgen ray therapy. I think that it is well to turn some of these cases over to men using heavily filtered roentgen ray, approaching radium in effect.

DR. MORRIS MARKOWITZ: I think that only about 10 or 15 per cent disappear spontaneously.

DR. HERBERT J. SMITH: I should like to suggest that repeated traumatism clears up these lesions. If the needle is simply thrust into the lesion repeatedly, it will clear up.

DR. THOMAS BUTTERWORTH, Reading, Pa.: Too often, I should say, treatment of these lesions with solid carbon dioxide gets one into trouble.

Iodide Dermatitis. Presented by DR. FRED D. WEIDMAN and DR. SIMON KATZ.

E. T., a well nourished white woman aged 23 years, presents a fungating circular lesion, of four weeks' duration, on the middle of the chin, associated with submental adenopathy. There is a punched-out ulcer on the right thigh. There is a pea-sized papule in each temporal region. There are three noneroded nodules on the labia. For the past three days the patient has been hoarse. For one month prior to the onset of the eruption, she took a small quantity of a solution of potassium iodide (exact dose unknown) once daily. The patient had previously received a course of treatment with oxophenarsine hydrochloride from Jan. 8, 1942, to Jan. 22, 1942. The serologic reaction of her blood was reported negative at various times from April 13, 1942, to June 29, 1942. On Sept. 12, 1945, it was reported positive (4 plus). Dark field examination of the serum from the lesion on the chin gave negative results. A complete blood cell count revealed a 63 per cent hemoglobin content, 3,760,000 erythrocytes, 6,200 leukocytes, 42 per cent neutrophils, 54 per cent lymphocytes and 4 per cent eosinophils.

There is a history of having received "injections in the hip" for a period of six months ending in March 1945. She has taken sodium chloride internally.

DISCUSSION

DR. FRED D. WEIDMAN: An interesting feature of this case is the occurrence of the nodules on the vulva. I should like to be informed about the frequency with which iodide lesions have been seen on the vulva.

DR. HERBERT J. SMITH: I never heard of an iodide eruption appearing on the vulva. I think that the lesions are syphilitic.

DR. SIMON KATZ: This patient has received thirty-seven injections of oxophenarsine hydrochloride and thirteen injections of a bismuth preparation. After she came home from the hospital, her mother thought that the best way to get rid of the infection was to give her iodide of potassium, and she gave her a glassful (of indeterminate dosage) every day. Since she has taken the iodide, the hoarseness, the eruption on the mucous membranes, the lesion on her chin and the submental adenopathy have developed.

DR. HERMAN BEERMAN: I think that it is iododerma. I have never seen iodide lesions on the vulva, but Dr. Greenbaum has reported oral lesions resulting from use of iodide. I do not see why this patient's clinical picture is inconsistent with a diagnosis of iododerma.

Book Reviews

Pathology of Tropical Diseases. By Col. J. E. Ash, M.C., A.U.S., Director, Army Institute of Pathology, Army Medical Museum, and Sophie Spitz, M.D., C.S., A.U.S., pathologist, Army Institute of Pathology, Army Medical Museum. Price, $8. Pp. 350, with 941 illustrations, 15 in color, on 257 plates. Philadelphia and London: W. B. Saunders Company, 1945.

Although this splendid manual was composed primarily for students of tropical medicine and naturally was written from the point of view of the pathologist, a surprisingly large part of it concerns dermatology. Since it is an atlas, an estimated 90 per cent of the pages consists of illustrations. The text, although naturally and necessarily abbreviated, is none the less thoroughly brought down to date; it is gratifying to observe the manner in which essential material can be condensed.

The senior author, Colonel Ash, has been active for a number of years in the educational program of the American Academy of Dermatology and Syphilology, and perhaps this association with dermatologists is partly responsible for the rich representation of dermatologic illustrations. One might indeed suspect that special effort had been made to assemble as many dermatologic illustrations as possible. There are few that are not original, and many are not paralleled elsewhere in print. Incidentally, this atlas is one more tangible expression of the manifold activities which have raised the Army Institute of Pathology to such an enviable place in American medicine.

The service to dermatology is directed where it is much needed, i. e., toward the etiologic agent and the histopathology, which have been given much emphasis. For example, there are scores of illustrations of aid in these respects in the text relating to smallpox, granuloma inguinale, lymphogranuloma venereum, verruga peruana, yaws, bejel, pinta and leprosy. Naturally, the dermatologist is also informed as to the osseous and visceral lesions in the premises.

Fungous diseases are exhaustively illustrated, in respect to not only the deep mycoses, as might be expected, but also the superficial ones. The beautiful histologic sections of bullous dermatophytid and of the fungus in sections of onychomycosis, tinea versicolor, tinea capitis, favus and moniliasis illustrate this point. The rich material concerning the deep mycoses again includes large numbers of illustrations of the cutaneous involvements. All the foregoing compliments apply to the subjects of leishmaniasis, ground itch, creeping eruption, onchoceriasis, pellagra, scabies, chigoe, tropical ulcer and ainhum, although in a more limited way.

It is to be regretted that the authors did not follow the "Standard Nomenclature of Disease" in speaking of lymphogranuloma venereum. They used the term "lymphopathia venereum"—which, incidentally, has incorrect Latin terminations.

The publishers have done splendidly their share of the work. The book is sturdily bound and is printed on enamel paper throughout. The reproduction is superlative. In short, all concerned have rendered a large service to dermatology, whether knowingly or not, by supplying so many and such splendid illustrations. These can well serve as examples of the quality and the composition which should be aimed at when authors are planning to submit illustrations for publication to medical journals.

Cosmetics and Dermatitis. By Louis Schwartz, M.D., and Samuel M. Peck, M.D. Price $4. Pp. 189, with 20 illustrations. New York: Paul B. Hoeber, Inc., 1946.

In this publication the authors have attempted to systematize the knowledge of cosmetics and their effects. They utilize the existing literature on the subject and their own wide personal experience to accomplish their purpose.

The early sections of the book are devoted to the anatomy and physiology of the skin and percutaneous absorption of materials locally applied. The subject of dermatitis from cosmetics, including a discussion of occupational dermatitis among hairdressers and beauticians, is covered. In this section also is a useful partial list of chemicals and initial materials and cosmetics in which they may occur which may cause dermatitis.

Most instructive, perhaps, is the large section of the book devoted to the many different types of applications intended for use on the skin, sample formulas of these substances and their action.

A readily accessible bibliography follows each chapter.

The book contains much information on an important subject and should be valuable to the dermatologist.

Treatment by Ion Transfer (Iontophoresis). By D. Abramowitsch, M.D., and B. Neoussikine, M.D. Price, $4.50. Pp. 200. New York: Grune & Stratton, Inc., 1946.

In the preface the authors state that the field of ion transfer has not received the careful and widespread application and evaluation which its preliminary results appear to warrant. They hope that the presentation of existing knowledge in this field will serve as a basis for further study and utilization of its possibilities.

This book has fourteen chapters, a fairly extensive bibliography and an index. The first part of the book, consisting of four chapters, discusses the historical development of ion transfer, the physical characteristics of the electric current, the effect of electrolytically introduced drugs and the methods of treatment. The second part of the book is divided into the use of iontophoresis in diseases of the nervous system, arthritis, lumbago and torticollis, scars and dermatologic conditions, diseases of the genitalia, diseases of the ear, nose and throat, ophthalmology, dentistry and miscellaneous conditions such as neoplasms, phlebitis and varicose ulcers.

In discussing iontophoresis in dermatologic conditions, which is the main interest of the reviewer, the authors cite on five pages reports from the literature on the results of iontophoresis. Thus, bromine ion transfer is reported beneficial in the treatment of pruritus of the perineum and the anus, a 10 per cent potassium iodide solution in poorly healing wounds and ulcers and a 10 per cent solution of zinc sulfate or copper sulfate in streptococcic and fungous infections of the skin. Iontophoresis is reported to be successful in the treatment of superficial scars by means of zinc and chloride or iodine.

The reviewer believes that the mere citing of beneficial reports from the literature will not convince the dermatologist of the value of iontophoresis. The only way to awaken enthusiasm in this modality is to report in detail the effect of iontophoresis in numerous cases and to compare the results with those obtained from treatment with simpler methods.

Diseases of the Skin: For Practitioners and Students. By George Clinton Andrews, M.D., Associate Clinical Professor of Dermatology, Columbia University College of Physicians and Surgeons. Third edition. Price $10. Pp. 937, with 971 illustrations. Philadelphia: W. B. Saunders Company, 1946.

The third edition of this excellent book has been thoroughly revised from beginning to end. It contains thirty-five chapters, each with an adequate bibliography at the end. As the author states, every page has been rewritten and more than sixty new diseases of the skin have been added.

One of the most useful features of any dermatologic textbook consists in the number and quality of illustrations. In this respect the book has a wealth of well chosen clinical and histologic photographs. With a few exceptions, they are excellent.

The author has taken unusual pains to follow the "Standard Nomenclature of Disease and Standard Nomenclature of Operations." This is a help to all students of dermatology.

The reviewer was pleased to note that the so-called mixed type of leprosy was not discussed, as many physicians now have expressed the opinion that this does not exist.

One of the new features of the book is a chapter by Mr. Braestrup on roentgen ray physics applied in dermatology.

The use of fairly heavy glazed paper throughout the book makes it possible to have good reproductions of illustrations. The book is well written and up-to-date and is highly recommended for dermatologists as well as students and general practitioners.

Venereal Diseases in General Practice. By Svend Lomholt, M.D. Price 25 s. Pp. 231, with 78 black and white and 39 colored illustrations. London: H. K. Lewis & Co., Ltd., 1946.

The book is a revised English edition of a Danish textbook on venereal diseases. This edition was completed immediately before the war and had just been printed when the German occupation of Denmark in 1940 broke off all communication between England and Denmark. The advances made in the treatment of venereal diseases, particularly the use of intensive methods of arsenical administration in syphilis, the use of fever therapy in gonorrhea and the use of penicillin in the treatment of both gonorrhea and syphilis, are outlined in a supplement to the general text.

In the discussion of syphilitic aortitis, exception may be taken to the simple statement that both arsphenamine and the metals are tolerated well, since this may be misleading; it is fairly generally accepted that more emphasis should be placed on initial treatment with metals and iodides prior to institution of arsenical therapy in the treatment of aortitis. The subject of false positive serologic reactions, discussed in the chapter dealing with the Wassermann test, is dealt with but briefly, since the ever-growing list of diseases and conditions in which positive serologic reactions of the blood occur is not mentioned; of the tropical diseases causing positive serologic reactions, pinta should also be included.

Dr. Lomholt has covered the field of venereal diseases in a clear and concise manner and admirably accomplishes his purpose to give a readily accessible presentation of the subject to the general practitioner. The publication should be well received by the specialist in this field. The illustrations are uniformly excellent.